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DOI:

[10.1016/j.kint.2021.02.040](https://doi.org/10.1016/j.kint.2021.02.040)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Karunanithy, N., Robinson, E. J., Ahmad, F., Burton, J. O., Calder, F., Coles, S., Das, N., Dorling, A., Forman, C., Jaffer, O., Lawman, S., Lakshminarayan, R., Lewlellyn, R., Peacock, J. L., Ramnarine, R., Mesa, I. R., Shaikh, S., Simpson, J., Steiner, K., ... Robson, M. G. (2021). A multicenter randomized controlled trial indicates that paclitaxel-coated balloons provide no benefit for arteriovenous fistulas. *Kidney International*, 100(2), 447-456. <https://doi.org/10.1016/j.kint.2021.02.040>

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Paclitaxel-coated balloons and angioplasty of arteriovenous fistulas (PAVE): a multicentre randomised controlled trial

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ABSTRACT

To assess the efficacy of paclitaxel-coated angioplasty balloons in prolonging the survival time of target lesion primary patency in arteriovenous fistulas, we designed an investigator-led multi-centre randomised controlled trial with follow up time variable and for a minimum of one year. Patients with an arteriovenous fistula who were undergoing an angioplasty for a clinical indication were included. Patients with one or more lesions outside the treatment segment were excluded. Following successful treatment with a high-pressure balloon, 212 patients were randomised. In the intervention arm, the second component was insertion of a paclitaxel-coated balloon; and in the control arm, an identical procedure was followed, but using a standard balloon. The primary endpoint was time to loss of clinically-driven target lesion primary patency. Primary analysis showed no evidence for a difference in time to end of target lesion primary patency between groups: hazard ratio (95% confidence interval) = 1.18 (0.78, 1.79), $p=0.440$. There were no significant differences for any secondary outcomes, including patency outcomes and adverse events. This study demonstrates no evidence that paclitaxel-coated balloons provide benefit, following standard care high-pressure balloon angioplasty, in the treatment of arteriovenous fistulas. In view of the benefit suggest by other trials, the role of paclitaxel-coated angioplasty balloons remains uncertain. Trial registration: ISRCTN14284759.

Keywords; Dialysis, arteriovenous fistula, angioplasty, fistuloplasty, paclitaxel

Introduction

Complications of vascular access are an important cause of morbidity and mortality in haemodialysis patients ¹. It is widely accepted that an arteriovenous fistula (AVF) is the optimal form of vascular access with better patency and lower infection rates than arteriovenous grafts (AVGs) and central venous catheters (CVCs) ². The initial therapy for a stenosis in an AVF is balloon angioplasty with high pressure as needed ³. A major concern however is the longevity of this effect. Retrospective studies have reported post-intervention primary patency rates of around 60-70% at 6 months and 40-50% at one year ⁴⁻¹⁰. Hence more durable interventions are required to reduce restenosis rates.

There has been recent interest in the use of paclitaxel-coated balloons to improve patency rates following angioplasty of AVFs. The role of paclitaxel-coated balloons has been established in the coronary and peripheral arterial circulations ^{11,12}. A number of small studies have explored the potential in arteriovenous fistulas ¹³⁻¹⁷. These included studies with AVGs in addition to AVFs ^{16,17}, and a study in central venous stenosis ¹³. Two larger randomised controlled trials in arteriovenous fistulas have been performed. One of these included 148 lesions and had an angiographic rather than clinical primary endpoint ¹⁸. The other randomised 132 lesions and had an ultrasonographic endpoint ¹⁹. In this second study, 48% of lesions contained an endovascular stent which complicates interpretation of the results. In both of these studies, more than one lesion per participant was included in the trial in some cases, which means that the observations were not independent.

Two large industry-sponsored randomised controlled trials have been performed and these provide the highest quality evidence to date. The first, by Treretola et al, enrolled 285 patients with AVFs from 23 centres ^{20,21}. There was no evidence that paclitaxel-coated balloon–assisted angioplasty was more effective at the primary end point, patency survival at 180 days, compared with conventional angioplasty. A second industry sponsored study, by Lookstein et al, enrolled 330 patients from 29 sites ²². The results showed that the primary endpoint of target lesion primary patency at 6 months was significantly greater in those treated with paclitaxel-coated balloons

(82.2% v 59.5%). The PAVE trial is the first investigator-led large scale randomised controlled trial designed to test the efficacy of paclitaxel-coated balloons in AVFs.

Methods

Patients and Trial Design

We performed a randomised controlled trial and aimed to recruit 211 patients (aged ≥ 18), referred with a clinical indication for angioplasty of an arteriovenous fistula, from 20 UK centres. Eligible patients were randomised (1:1) post-fistuloplasty to inflation of a second low-pressure balloon which was either paclitaxel-coated or standard (non-coated) by the King's Clinical Trials Unit using a web-based system. Randomisation was minimised according to the Interventional Radiologist performing the procedure and two binary factors: previous radiological intervention (yes/no); and patient on haemodialysis at study entry (yes/no). The allocation was masked from patients, the clinicians responsible for referral to Interventional Radiology, and the research team including trial statisticians. The treating radiologist could not be masked to treatment allocation due to the appearance of the paclitaxel-coated balloon.

If the access circuit contained synthetic graft material or stents, synchronous lesion(s) outside the treatment segment, thrombosis, central vein stenosis or residual stenosis $\geq 30\%$ after high-pressure balloon fistuloplasty, the patient was excluded²³. Protocol changes in March 2016 and July 2016 broadened the eligibility criteria to include in turn, patients who had not yet started haemodialysis and patients with a treatment segment containing one or more lesions that could be treated with a single drug-coated balloon up to 120mm in length. These changes were made to aid recruitment, whilst maintaining the requirement for an absence of lesions outside the treatment segment, which was a unique feature of the trial. A log of changes to inclusion and exclusion criteria is available in supplementary material S1 with trial oversight detailed in supplementary material S2. Full details of inclusion and exclusion criteria are also in the original and final protocols (supplementary material S7). Patients were followed up for a minimum of one year, and all patients continued in the study until the last patient had completed one year of follow up. All patients gave informed consent, and the trial was approved by the London-Chelsea Research Ethics Committee 15/LO/0638.

Treatments

Following the pre-procedure fistulogram the operating radiologist assessed if the patient remained

eligible. For all patients the treatment had two components. Firstly, the fistuloplasty procedure was performed with a high-pressure balloon (Bard Dorado), with inflation up to 24 atmospheres to ensure obliteration of the lesion waist, according to the study protocol. Following this, inclusion and exclusion criteria were rereviewed prior to randomisation. In the intervention arm, the second component was insertion of a paclitaxel-coated balloon (Bard Lutonix); and in the control arm, an identical procedure was followed, but using a standard balloon (Bard Ultraverse).

Outcomes

The primary endpoint was time (days) to loss of target lesion primary patency. This was defined as patency with no re-intervention to the area 5 mm proximal to, within, and 5 mm distal to, the index treatment segment. Target lesion primary patency ended when any of the following occurred: (a) clinically driven re-intervention to the treatment segment; (b) thrombotic occlusion that includes the treatment segment; (c) surgical intervention that excludes the treatment segment from the access circuit; (d) abandonment of the AVF due to an inability to retreat the treatment segment. In order to minimise bias, a different interventional radiologist to the one who performed the index procedure performed repeat procedures whenever possible. Secondary patency endpoints were time to loss of access circuit primary patency, and time to loss of access circuit cumulative patency. Access circuit primary patency ended when any of the following occurred: (a) access circuit thrombosis, (b) an intervention (either radiological or surgical) anywhere in the access circuit, or (c) the access circuit is abandoned due to an inability to treat any lesion. Access circuit cumulative patency ends when the AVF is abandoned, regardless of radiological or surgical intervention, with or without a thrombosis event. Multiple/repetitive treatments for stenoses that restore patency are compatible with cumulative patency. Other pre-specified secondary endpoints were: angiographically determined late lumen loss (mm), rate of binary angiographic re-stenosis (%), procedural success (stenosis \leq 30% at completion fistulogram II), number of thrombosis events, fistula interventions, adverse events during follow-up, and patient quality of life assessed using POS-S renal scores and EQ-5D-5L scales at 6- and 12-months post randomisation. Further detail on the primary and secondary endpoint definitions are in the original and final protocols (supplementary material S7). Angiographic secondary endpoints core lab analysis was performed by the Cardiovascular European Research Centre (Massy, France).

Statistics and analysis

The sample size and power calculations have been described fully in the published protocol²³ and in the statistical analysis plan which was signed off prior to database lock. To test the superiority of the paclitaxel-coated balloon compared to the standard balloon in time to loss of target lesion primary patency (TLPP), Cox proportional-hazards regression was used with treatment group and the two binary minimisation factors as covariates. The third minimisation factor, interventional radiologist performing the study procedure, was not adjusted for as this would not allow enough degrees of freedom. Analysis was by intention to treat. Patients were censored if: they had TLPP survival at the end of follow up; or received a renal transplant, switched to peritoneal dialysis, died or withdrew from further data collection before reaching the primary endpoint, prior to the study end. Schoenfeld residuals were assessed to test whether the proportional-hazards assumption was violated; and an interaction term between treatment group and (log)time was considered to allow for variable follow-up time effects, if they existed. Multiple imputation was considered if numbers of patients non-compliant with study treatment or lost to follow-up were notable or uneven across treatment groups

Planned secondary and sensitivity analyses included: an adjusted analysis of the primary outcome to evaluate the impact of pre-specified baseline covariates on the estimated treatment effect; and an analysis using deaths (not relevant to primary endpoint) and transplantation as competing risks rather than censored events to evaluate the influence of the competing events from preventing the primary endpoint being observed. For the former, the baseline variables were: ethnicity; age; diabetes diagnosis; smoking history; total time (quartiles) on haemodialysis; type of native fistula (where the one patient with radial ulna loop was excluded); previous surgical intervention to the access circuit; and location of stenosis (where the smallest two categories, cephalic arch and after cephalic arch but not beyond the thoracic inlet, were merged due to low sub-group numbers).

Time to event secondary outcomes were analysed using the same Cox proportional-hazards regression. Continuous outcomes employed multiple linear regression, again adjusting for the two binary minimisation factors, as well as baseline measures of the outcome, if relevant. Count

outcomes (checked for over-dispersion) were analysed using negative binomial regression, with time in trial set as the exposure period. Results are reported as hazard ratios, regression coefficients, odds ratios, or incidence rate ratios, with 95% confidence intervals, where appropriate. Kaplan-Meier survival curves were constructed by treatment group to illustrate the time to loss of the three patency endpoints. Adverse events were categorised into relevant types for this patient population (for example, access-related or not), and a stacked bar-chart of maximum severity was used to visually compare treatment groups where patients had reported at least one event. Analysis was done using Stata version 16.0 (StataCorp, Texas).

Results

Patients

Between 16 November 2015 and 4 October 2018, 212 patients from 20 UK centres (supplementary material S3) were randomised into the trial (106 paclitaxel-coated balloon and 106 standard balloon) (Figure 1). The trial ended on 4 October 2019 when all patients had completed at least one year of follow up. Baseline patient demographics and medical history are reported in Table 1 and supplementary material S4-S5 (smoking, renal replacement therapy history and quality of life). The proportion of patients in both the paclitaxel-coated and standard balloon groups who were male (63.2 and 57.5%), Caucasian (77.4% and 67.9%), had diabetes (54.7% and 43.3%), or coronary artery disease (23.6% and 28.3%) reflects the population receiving haemodialysis in the UK, as does the mean age (66.9 and 64.1). Although we included patients who had not yet started dialysis, the large majority (88.7% and 91.5%) were receiving haemodialysis. In 79.2% and 77.4% of cases the fistula had been used. In the remainder, the intervention was performed to aid fistula maturation or blood flow prior to use for haemodialysis. There was a range of indications for intervention that are in keeping with clinical experience (Table 1). All characteristics including fistula type and lesion location appeared balanced between the groups. A specific high-pressure balloon (Bard Dorado) is named in the protocol. There were no differences in frequency of its use or in the lengths of the high-pressure and treatment balloons used. Two patients did not receive their allocated treatment (paclitaxel-coated balloon) because they were found to be ineligible after randomisation, but they were both included in the intention-to-treat analysis (denoted by dashed lines in Figure 1). The inflation time of the treatment balloon was as specified in the protocol in 100% and 94% of cases in the paclitaxel-coated and standard balloon groups, respectively. There were no other major protocol deviations. Six patients withdrew from further data collection during follow-up and were censored in the primary analysis; no patients were lost to follow-up. Multiple imputation was not necessary.

Outcomes

Only one (out of a possible three) interim analysis was conducted during the trial, when number of primary endpoint events had reached 27 and recruitment was still ongoing. The independent data monitoring and ethics committee reviewed partially-masked results and recommended the

continuation of the trial as the pre-specified futility and efficacy boundaries had not been met. At the end of the study 89 patients had reached the primary endpoint loss of target lesion primary patency (TLPP) over the trial period, with similar numbers in each treatment group: 44 in the paclitaxel-coated balloon group and 45 in the standard balloon group (Table 2; Figure 2A). For those who lost TLPP, the median (IQR) times to event (in days) were similar at 159 (102-234) and 215 (145-340). There was no evidence of a difference in time to loss of TLPP in the paclitaxel-coated balloon group compared to the standard balloon using Cox proportional-hazards regression (hazard ratio 1.18 (95% CI: 0.78, 1.79), $p=0.440$; Table 2), and there was no suggestion that variable follow-up time effects needed to be adjusted for. The results were not appreciably different in the secondary adjusted analysis, including baseline covariates (HR (95% CI): 1.11 (0.69, 1.78), $p=0.664$), or in the competing risks sensitivity analysis (sub-hazard ratio (95% CI): 1.06 (0.67, 1.67), $p=0.805$). All patients randomised in the current trial were included in the final intention-to-treat survival analysis and no patients were lost to follow-up so there were no missing primary outcome data.

At 6 months the TLPP was 71.7% (66/92 patients) in the paclitaxel-coated balloon group, compared to 84.5% (82/97 patients) in the standard balloon group. By 12 months, these figures were 52.5% (44/81) and 58.8% (50/85) respectively. Radiological reintervention was the reason for meeting the primary endpoint in 31 (70.5%) and 34 (75.6%) of the paclitaxel-coated and standard balloon groups, respectively. In only one quarter (17/65) of cases was the primary endpoint met due to reintervention by the interventional radiologist who performed the index procedure, which was evenly split across treatment groups (8 paclitaxel-coated and 9 standard balloon). Otherwise, the primary endpoint was reached due to: thrombosis (3 (6.8%) and 5 (11.1%)); surgical intervention (5 (11.4%) and 1 (2.2%)); or a decision to abandon the fistula (5 (11.4%) and 5 (11.1%)) of paclitaxel-coated and standard balloon groups, respectively. Out of 46 fistulas that had not yet been used for dialysis, only 10 (21.7%) of these were abandoned (having reached the end of access circuit cumulative patency) during follow up

For the two time to event secondary outcomes of loss of access circuit primary and cumulative patency there was again no evidence for a difference between the treatment groups: HR (95% CI):

1.06 (0.71, 1.59), $p=0.764$; and HR (95% CI): 1.30 (0.67, 2.55), $p=0.438$, respectively (Table 2; Figures 2B-2C). None of the other secondary outcomes demonstrated a treatment effect of paclitaxel-coated balloon compared to standard balloon: (Table 2) mean late lumen loss was 1.49mm and 1.48 mm; binary restenosis at 6 months occurred in 62.5% and 57.7%; and procedural success (residual stenosis <30% after treatment with paclitaxel-coated or standard balloon) occurred in 98.1% and 92.5%. Data for the number of thrombosis events, fistula interventions, adverse events, and quality of life at 6 and 12 months are also given in Table 2 and were similar in both groups. Further data on quality of life at 6 and 12 months are given in supplementary material S5 with a list of adverse events in supplementary material S6. All relevant model assumptions were checked and considered compliant. Finally, Figure 3 illustrates the maximum severity for reported adverse events, where a patient had at least one event for each respective category. In total, 216 events were reported during the study (113 paclitaxel-coated balloon vs 103 standard balloon), including: 32 deaths (18 vs 14) and 59 access-related events (36 vs 23).

Discussion

The aim of the PAVE trial was to assess the efficacy of paclitaxel-coated balloons in the treatment of arteriovenous fistulas used to deliver haemodialysis. Although a number of earlier studies have suggested a possible benefit ¹³⁻¹⁹, there are only two previous large randomised trials, with clinical endpoints, addressing this question ^{20 22}. The first published large-scale trial by Treretola et al, using the same paclitaxel-coated balloon as the current trial, also failed to demonstrate a difference between arms in their pre-specified primary endpoint, target lesion primary patency at 180 days ²⁰, but there was a significant difference at 210 days in an exploratory analysis. A later publication from this same study showed a significant difference at 12 months but not at 24 months ²¹. Therefore, uncertainty remained regarding the efficacy of paclitaxel-coated balloons for this indication.

A recent study by Lookstein et al that also used a binary primary endpoint of target lesion primary patency at 6 months did find evidence of a benefit for paclitaxel-coated balloons ²². One possible explanation for the contrasting result in this and the current study is the use of a different treatment balloon. The Lutonix balloon used in the current study used a coating of paclitaxel, sorbitol and polysorbate with a drug dose density of $2\mu\text{g}/\text{mm}^2$. In contrast the IN.PACT balloon used by Lookstein et al is loaded with a higher concentration of paclitaxel ($3.5\mu\text{g}/\text{mm}^2$) and uses a urea-based excipient. These devices were compared in a pig femoral artery angioplasty model ²⁴. There was no comparison of the amount of drug delivered to the artery. However, there was a higher paclitaxel content in non-target tissues and evidence of downstream embolic crystalline material with the IN.PACT balloon. Another study showed greater drug loss from the IN.PACT balloon than from the Lutonix balloon with dry handling or inflation ²⁵. Therefore, the higher drug dose density on the IN.PACT balloon does not necessarily result in a higher drug dose being delivered to the target lesion because a higher proportion may be lost before insertion or deposited in non-target tissues.

When recruitment to the PAVE trial began in November 2015, the instructions for the paclitaxel-coated balloon recommended an inflation time of 30 seconds and 60 seconds was stated in the protocol to ensure this was exceeded. Data collected during the trial included a question asking if

an inflation time of more than 60 seconds was achieved (yes or no). From March 2018, when 75% of patients had been randomised, study sites were asked to inflate for a minimum of 120 seconds following a change in the manufacturer's instructions. The data in table 1 showed good adherence to the protocol with inflation recorded as more than 60 seconds in 97% of patients, with no evidence of a difference between groups. The manufacturer's recommendation for an increase in inflation time is based on preclinical data in a pig femoral artery angioplasty model, but there are no data given comparing 60 and 120 seconds²⁵. The fact that the current study used the Lutonix balloon with a minimum inflation time of 60 seconds, does not necessarily mean that a lower dose of paclitaxel was delivered to the target lesion that occurred in the study by Lookstein et al using the IN.PACT balloon²². However, we acknowledge that this is a possible explanation for the differing results.

A limitation of the PAVE trial is that it was not a fully blinded trial. It was impossible to ensure that treating radiologists were blinded to treatment allocation due to the appearance of the paclitaxel-coated balloon. However, all other investigators as well as the patients were blinded and this minimised the chance of bias. Furthermore, it is more likely that any small introduction of bias would have led to a positive outcome, rather than the negative result that we found. Patients were invited to attend a 6 month protocol fistulogram. If clinically-indicated imaging or intervention was planned then the protocol fistulogram was not requested. Radiologists were instructed not to intervene if subclinical stenosis were detected at the protocol fistulogram and this was adhered to in all cases. Therefore, the protocol fistulogram had no effect on the primary outcome measure of clinically-driven TLPP.

A number of aspects in the design of the current trial further reduced the possibility of bias. Reintervention was only performed after referral for a clinical indication by a member of the clinical team blinded to the treatment allocation. Clinically driven radiological reintervention was the predominant reason for meeting the primary endpoint. Reintervention was performed by a different interventional radiologist whenever possible. Images from radiological interventions leading to loss of target lesion primary patency were reviewed by an interventional radiologist from a different study site or the core laboratory in all cases. In cases where the primary endpoint was

reached due to surgical intervention or a decision to abandon the fistula, the decision would not have been influenced by knowledge of treatment allocation.

The 6-month TLPP in the control group was 71.1% in the current trial and this is higher than those reported in the other published trials^{20,22} and most institutional case series⁴⁻¹⁰. The TLPP in the control arm of the study by Lookstein et al was only 59.5% at 6 months²². This underlines the value of a good balloon fistuloplasty in maintaining patency. If a good result is achieved with a high-pressure plain balloon, then there may be little or no benefit in using an additional paclitaxel-coated balloon. This may be why paclitaxel-coated balloons were shown to improve the outcome in the study by Lookstein et al²², but not in the current study. An increase in mortality has been linked with the use of paclitaxel coated balloons in peripheral vascular disease²⁶. An effect was seen after 2 years but not after one year and the mechanism was not clear. Although we saw more deaths in patients treated with paclitaxel-coated balloons compared with the control group (Figure 3), the difference was small, and the numbers too low to draw any conclusions.

In contrast to the previous trials^{20,22} only patients with a single lesion or tandem lesions that could be treated by a single drug-coated balloon, were eligible in the current trial. This is unlikely to explain the lower event rate in the current trial because previous data suggests that post-intervention access circuit primary patency is similar in patients with multiple or single lesions⁷. However, stenoses at multiple sites in the access circuit is a common finding and deciding which is clinically most significant can be subjective. We therefore only included patients with a stenosis at a single site in the circuit in order to be sure that this lesion was responsible for the clinical problem leading to intervention. In order to maintain recruitment of patients with a single treatment segment, we included fistulas that had not yet been used for dialysis. However, few of these were abandoned (having reached the end of access circuit cumulative patency) during follow up. Therefore, a high rate of primary failure of fistula maturation was unlikely to affect the outcome. We consider that the application of a drug coated balloon to a single treatment segment to be a unique feature and a strength of the current study^{20,22}. The aim was to investigate the efficacy of paclitaxel-coated balloons and we believe that this increased the rigour with which we were able to address this aim.

In conclusion, the current results provide no evidence of an additional benefit from paclitaxel-coated balloons compared to standard balloons when used after a clinically driven high-pressure balloon angioplasty in arteriovenous fistulas. We did not observe any indication of an early treatment effect in the data, and all of the pre-specified outcomes support the same conclusion.

Disclosure

KS has performed consultancy work and sat on an advisory board for CR Bard (Becton Dickinson). None of the other authors have any conflicts of interest to declare.

Data sharing

Deidentified participant data will be made available following publication to researchers with a methodologically sound proposal. Proposals should be directed to the corresponding author.

Supplementary Material

Section S1 Inclusion and exclusion criteria

Section S2 Trial oversight

Section S3 Sites

Section S4 Baseline smoking and renal replacement therapy history

Section S5 Health-related Quality of Life

Section S6 List of adverse events

Section S7 Protocols and statistical analysis plans:

 Original protocol (version 2.0, approved before the first site opened)

 Final protocol (version 9.0)

 Version control document (summary of changes)

 Original statistical analysis plan (version 1.0)

 Second and final statistical analysis plan (version 2.0, changes listed in section 1.6)

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Acknowledgements

This project (Project 13/94/10) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The views expressed in this publication are those of the authors and not necessarily those of the MRC, NIHR or the Department of Health and Social Care. High Pressure, Drug-coated, and control balloons were supplied by CR Bard (Becton Dickinson and Company) who had no other role in the study. EJR received salary support from the NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. We are grateful to Vikki Semik, Charlotte Bailey and Micheala Curran for work on trial management, to Konstantinos Katsanos for work in planning the study, and to members of the data monitoring and trial steering committees. These committee members were Duncan Ettles, Richard Haynes, Thomas Hiemstra, Peter Littler, Andrew McGrath, Sandip Mitra, David Oliviera, Nick Palmer, Uday Patel, Isabel Reading, Max Troxler, Christopher Watson and Andrew Wigham. Further details on committee members are in supplemental material S2. We are grateful to the numerous people at study sites, in both research and clinical roles, who contributed to this study. We are also grateful to all of the patients who consented to participation.

Table 1. Baseline demographic, clinical and treatment characteristics of the intention-to-treat population

		Paclitaxel-coated balloon (n=106)	Standard balloon (n=106)
		n (%) unless stated	
Age	mean (SD)	66.9 (12.7)	64.1 (13.3)
Sex	Male	67 (63.2)	61 (57.5)
Ethnicity	White	82 (77.4)	72 (67.9)
	Black	9 (8.5)	16 (15.1)
	Asian	11 (10.4)	14 (13.2)
	Mixed/Other	4 (3.8)	4 (3.8)
Current diabetes diagnosis	Yes	58 (54.7)	46 (43.4)
Coronary artery disease	Yes	25 (23.6)	30 (28.3)
Peripheral vascular disease	Yes	13 (12.3)	18 (17.0)
Currently on haemodialysis [†]	Yes	94 (88.7)	97 (91.5)
Location of fistula (arm)	Left	84 (79.2)	72 (67.9)
Type of native fistula	Radio-cephalic	43 (40.6)	39 (36.8)
	Brachio-cephalic	52 (49.1)	55 (51.9)
	Basilic vein transposition	10 (9.4)	12 (11.3)
	Radial ulna loop	1 (0.9)	NA
Time since fistula formed (months) (n=210)	median (IQR)	23 (8-40)	16 (7.5-40.5)
Fistula been used at least once	Yes	84 (79.2)	82 (77.4)
Time since fistula was first used (months) (n=166) [‡]	median (IQR)	21 (7-41)	15 (5-36)
Current access circuit previously had a thrombosis	Yes	7 (6.6)	3 (2.8)
Previous surgical interventions to the current access circuit	Yes	20 (18.9)	24 (22.6)
Previous radiological intervention in access circuit [†]	Yes	35 (33.0)	38 (35.8)
Location of stenosis	Juxta-anastomotic	51 (48.1)	43 (40.6)
	Venous segment*	40 (37.7)	51 (48.1)
	Cephalic arch	15 (14.2)	10 (9.4)
	From cephalic arch to thoracic inlet	-	2 (1.9)
Primary indication for the index procedure	Inadequate dialysis	12 (11.3)	6 (5.7)
	Poor blood flow	37 (34.9)	37 (34.9)
	Prolonged bleeding	5 (4.7)	9 (8.5)
	High venous pressure	9 (8.5)	11 (10.4)
	Low arterial pressure	-	1 (0.9)
	Difficulty needling	25 (23.6)	20 (18.9)
	Immature fistula	5 (4.7)	6 (5.7)
	Not specified	11 (10.4)	13 (12.3)
	Other	2 (1.9)	3 (2.8)
High pressure balloon type as per protocol	Yes	87 (82.1)	85 (80.2)
High pressure balloon length (cm)	mean (SD)	4.6 (1.7)	4.6 (1.8)
Treatment balloon length (cm)	mean (SD)	6.8 (2.0)	6.6 (1.9)
Treatment balloon inflation time > 1 minute	Yes	104/104 (100)	100/106 (94)

[†]Minimisation factor; [‡]If used at least once prior to randomisation; SD: standard deviation; IQR: inter-quartile range. * Draining vein (not just the cannulation segment)

Table 2. Descriptive summaries and formal between-group comparisons of the primary and secondary outcome measures

		Paclitaxel-coated balloon (n=106)	Standard balloon (n=106)	Estimated treatment group difference (95% CI)	p-value
Primary outcome		n (%) unless stated			
Time to loss of target lesion primary patency	Endpoint reached	44 (41.5)	45 (42.5)	HR: 1.18 (0.78, 1.79)	0.440
	median days (IQR)	159 (102-234)	215 (145-340)		
Secondary outcomes		n (%) unless stated			
Time to loss of access circuit primary patency	Endpoint reached	47 (44.3)	51 (48.1)	HR: 1.06 (0.71, 1.59)	0.764
	median days (IQR)	160 (94-268)	203 (139-324)		
Time to loss of access circuit cumulative patency	Endpoint reached	19 (17.9)	16 (15.1)	HR: 1.30 (0.67, 2.55)	0.438
	median days (IQR)	201 (85-359)	270.5 (173.5-383.5)		
Angiographically determined late lumen loss (mm)*	mean (SD)	1.49 (1.55) n=55	1.48 (1.68) n=50	0.17 (-0.38, 0.72)	0.541
Angiographic re-stenosis (≥50%)*	Yes	35 (62.5) n=56	30 (57.7) n=52	OR: 1.23 (0.56, 2.71)	0.600
Procedural success	Yes	102 (98.1) n=104	98 (92.5) n=106	OR: 4.16 (0.85, 20.37)	0.079
Number of thrombosis events	0	87 (82.1)	91 (85.8)	IRR: 1.58 (0.70, 3.58)	0.273
	1	16 (15.1)	10 (9.4)		
	>1	3 (2.8)	5 (4.7)		
Number of fistula interventions	0	55 (51.9)	53 (50.)	IRR: 1.26 (0.85, 1.87)	0.245
	1	25 (23.6)	32 (30.2)		
	>1	26 (24.5)	21 (19.8)		
Number of adverse events	median (IQR)	0 (1-2)	0 (0-2)	IRR: 1.26 (0.78, 2.04)	0.338
Health today (EQ-5D-5L VAS) 6-months	mean (SD)	64.4 (21.0) n=68	63.9 (20.5) n=74	0.32 (-5.25, 5.89)	0.909
Health today (EQ-5D-5L VAS) 12-months	mean (SD)	65.9 (20.2) n=48	66.0 (22.2) n=47	-1.79 (-9.40, 5.81)	0.640
POS-S Renal 6-months	mean (SD)	13.6 (10.8) n=68	13.6 (8.6) n=72	1.01 (-1.59, 3.60)	0.443
POS-S Renal 12-months	mean (SD)	13.9 (10.5) n=48	13.6 (8.1) n=47	2.07 (-0.49, 4.62)	0.111

*For those that required an intervention before 6 months, mean days to intervention were 125.1 in the paclitaxel-coated balloon group (n=23) and 149.6 in the standard balloon group (n=17); IQR: inter-quartile range; SD: standard deviation; HR: hazard ratio; OR: odds ratio; IRR: incidence rate ratio; EQ-5D-5L VAS: EuroQol-5 dimension-5 level visual analogue scale; POS-S: palliative outcome scale-symptom.

Figure legends

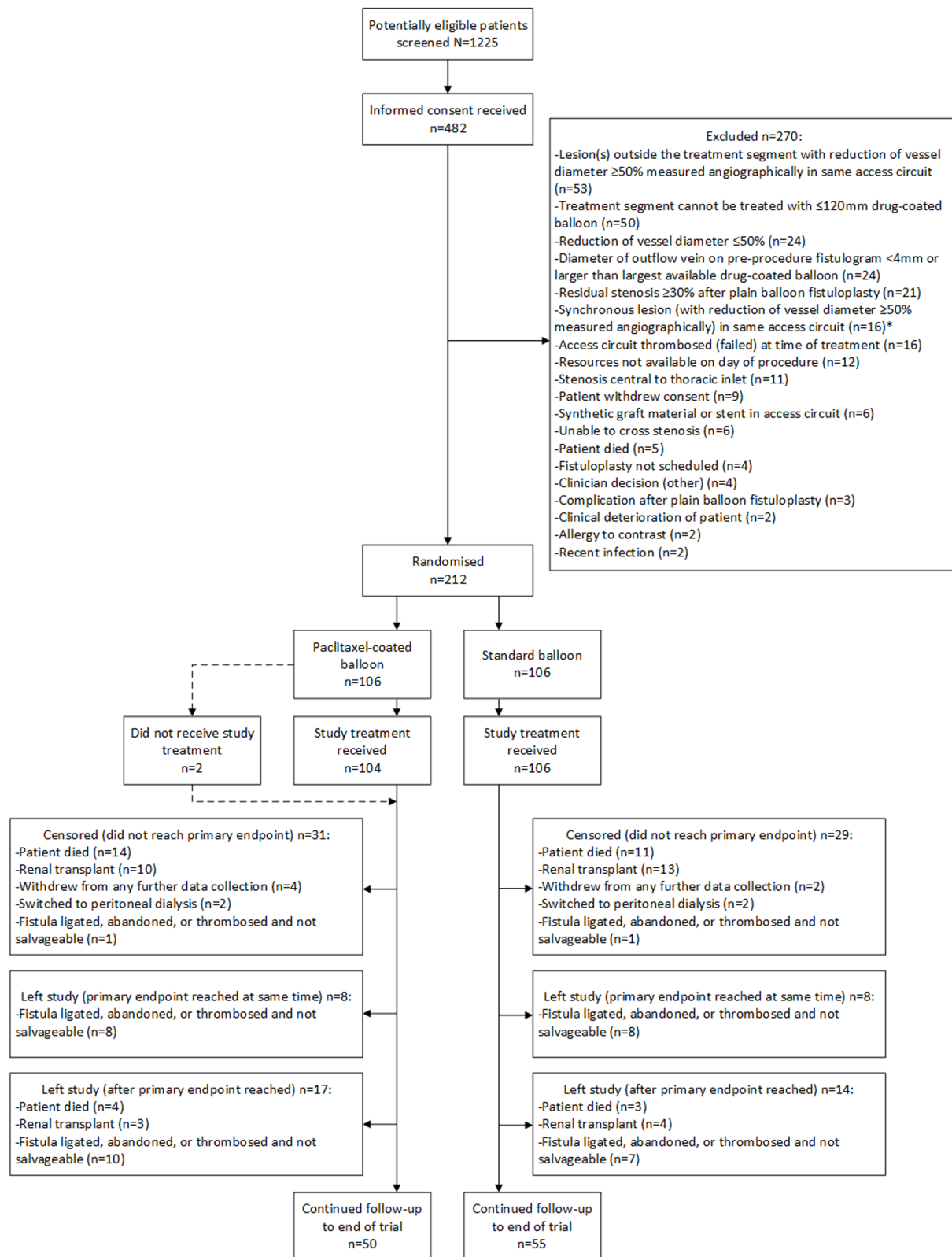


Figure 1.

CONSORT diagram

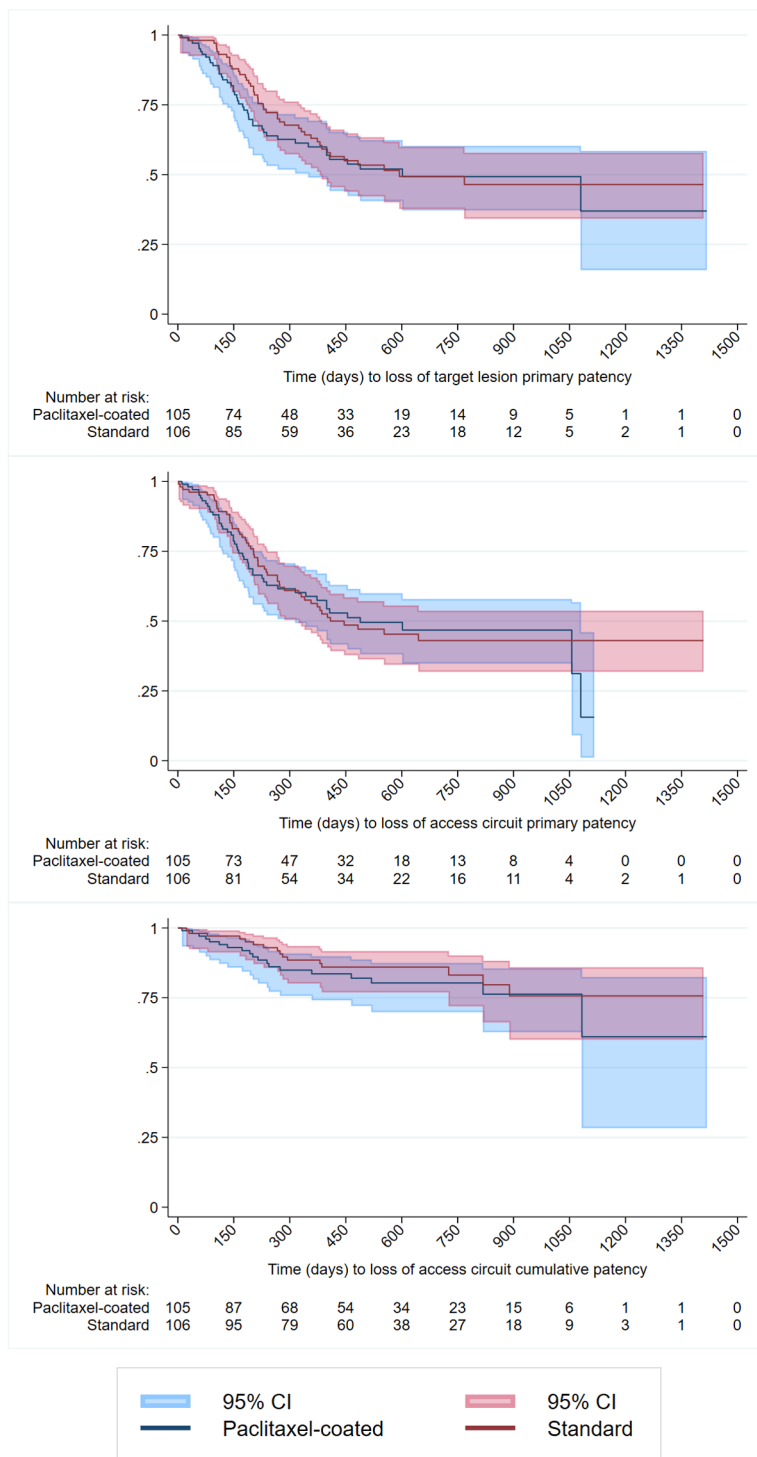


Figure 2.

Kaplan-Meier survival curves by treatment group for the loss of patency outcomes

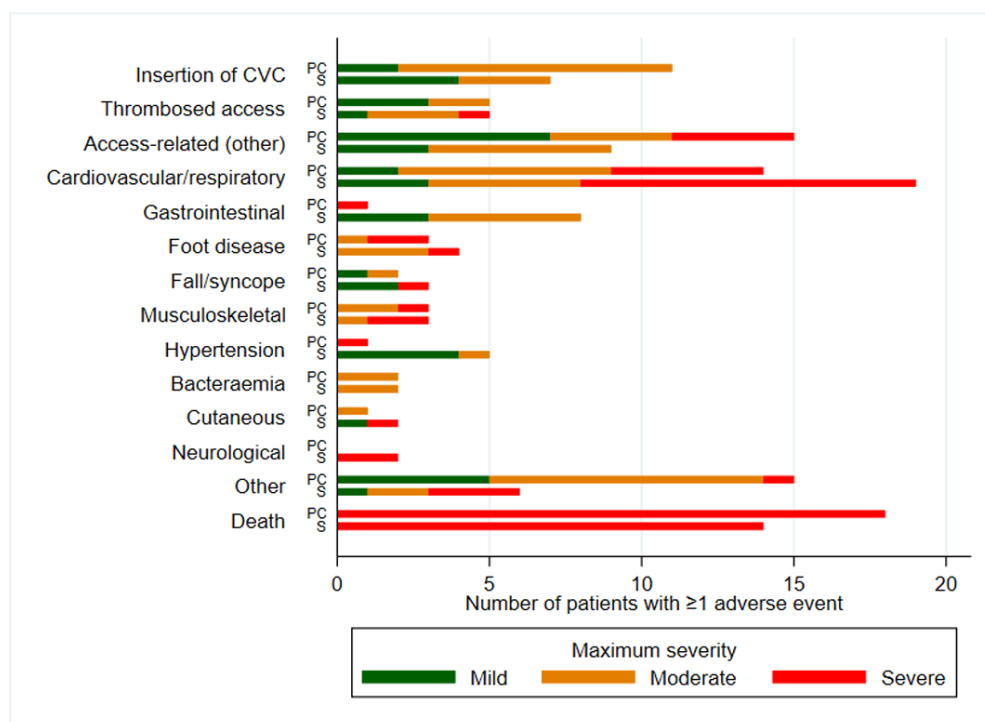


Figure 3.

Severity and type of adverse event by treatment group. PC: paclitaxel-coated balloon group; S: standard balloon group. This bar chart illustrates the main types of adverse events that were reported by patients during follow-up, by treatment group and maximum severity. Patients can be included in more than one type of event, but if they experienced a certain event type more than once, then they have only been counted once for that event, and the maximum severity that they reported for that type of event has been used. Please note: this graph does not include deaths that occurred after patients formally withdrew from the trial; CVC: central venous catheter.

Supplementary material

Section S1 Inclusion and exclusion criteria

Section S2 Trial oversight

Section S3 Sites

Section S4 Baseline smoking and renal replacement therapy history

Section S5 Health-related Quality of Life

Section S6 List of adverse events

Section S7 Protocols and statistical analysis plans:

Original protocol (version 2.0, approved before the first site opened)

Final protocol (version 9.0)

Version control document (summary of changes)

Original statistical analysis plan (version 1.0)

Second and final statistical analysis plan (version 2.0, changes listed in section 1.6)

S1 Inclusion and exclusion criteria

Protocol version 2 (approved 18.8.15, before recruitment started)

Inclusion criteria

1. Patients (18 years or over) who have a native AVF in the arm that has been used for haemodialysis for at least 12 dialysis sessions
2. An indication for a fistuloplasty as determined by the local clinical team
3. The access circuit is free of synthetic graft material or stents
4. A reduction of vessel diameter of $\geq 50\%$ measured angiographically, and a reference diameter of the outflow vein of at least 4 mm and less than the size of the largest available drug-coated balloon
5. A residual stenosis $\leq 30\%$ after plain balloon fistuloplasty

Exclusion criteria

1. Patient unable to give informed consent
2. Patient unwilling or unable to comply with all study-related procedures
3. Systemic or local (to the fistula) infection treated for less than 10 days prior to the study procedure
4. Synchronous venous lesion, with a reduction of vessel diameter of $\geq 50\%$ measured angiographically, in the same access circuit
5. Location of stenosis beyond the thoracic inlet
6. Thrombosed (failed) dialysis circuit at time of treatment
7. Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children, within two years of study treatment
8. Known hypersensitivity or contraindication to contrast medium which cannot be adequately premedicated
9. Known hypersensitivity or contraindication to paclitaxel

Protocol version 5 (approved 8.4.16)

Inclusion criteria 1 amended:

1. Patients (18 years or over) who have a native AVF in the arm

Protocol version 6 (approved 31.8.16)

Inclusion criteria 6 added:

6. A treatment segment, containing one or more lesions, which can be treated with ≤ 120 mm of a single drug-coated balloon.

Exclusion criteria 4 amended:

4. One or more lesions outside the treatment segment, with a reduction of vessel diameter of $\geq 50\%$ measured angiographically, in the same access circuit.

Protocol version 7 (approved 21.3.17)

Exclusion criteria 4 amended again:

4. One or more lesions outside the treatment segment, with a reduction of vessel diameter of $\geq 50\%$ measured angiographically, in the same access circuit. The patient will also be excluded if any lesions outside the treatment segment are treated even if these are $< 50\%$

S2 Trial Oversight

Data Monitoring Committee

Chair	Watson, Christopher ¹	University of Cambridge	25/04/2017 - current
Member	Hiemstra ² Thomas	University of Cambridge	Added 11/08/2018 - current
Member	Reading, Isabel ³	University of Southampton	Original Member
Resigned Chair	Oliviera, David ²	St George's University of London	Original - 25/04/2017
Resigned Member	Ettles, Duncan ⁴	Hull and East Yorkshire Hospitals NHS Trust	Original - 25/04/2017
Resigned Member	Wigham ⁴ , Andrew	John Radcliffe Hospital NHS Trust	25/04/2017 - 11/08/2018

Trial steering committee

Chair	Haynes, Richard ²	University of Oxford	Original Member
Member	McGrath, Andrew ⁴	Beaumont Hospital, Dublin, Ireland	Added 25/04/2017 - current
Member	Troxler, Max ¹	Leeds Teaching Hospital NHS Trust	Original Member
Public Member	Palmer, Nick ⁵	National Kidney Federation	Original Member
Member	Mitra, Sandip ²	Manchester University NHS Foundation Trust	Original Member
Resigned Member	Patel, Uday ⁴	St George's Healthcare NHS Trust	22/07/2016 - 25/04/2017
Resigned Member	Littler, Peter ⁴	The Newcastle Upon Tyne Hospitals NHS Foundation Trust	Original Member - 22/07/2016

1 Transplant and vascular access surgeon

2 Nephrologist

3 Statistician

4 Interventional radiologist

5 Patient representative

S3 Sites

Table: Hospital sites (radiologists per site)

Radiologist performing the treatment was a minimisation factor.

	Paclitaxel-coated balloon (n=106)	Standard balloon (n=106)
1. Bradford (1)	2	2
2. Cardiff (2)	5	3
3. Canterbury (2)	14	16
4. Edinburgh (2)	3	-
5. Gloucester (2)	8	8
6. Guy's (9)	21	16
7. Hull (3)	4	5
8. King's (4)	4	8
9. Leicester (1)	2	2
10. Lister (2)	11	10
11. Portsmouth (2)	5	2
12. Devon (2)	4	3
13. Royal London (1)	1	3
14. Reading (2)	5	4
15. Royal Free (3)	3	5
16. Preston (2)	2	3
17. Brighton (1)	1	1
18. Sheffield (2)	1	1
19. St George's (1)	1	2
20. St Helier (1)	9	12

S4 Baseline smoking and renal replacement therapy history of the intention-to-treat population

		Paclitaxel-coated balloon (n=106)	Standard balloon (n=106)
		n (%) unless stated	
Patient smoking history (n=211)	Current	12 (11.4)	16 (15.1)
	Former	37 (35.2)	33 (31.1)
	Never	56 (53.3)	57 (53.8)
Total accumulated time patient has spent on haemodialysis (months; quartiles) (n=211)	0-6 months	29 (27.4)	26 (24.8)
	7-17 months	20 (18.9)	31 (29.5)
	18-39 months	31 (29.2)	23 (21.9)
	40-198 months	26 (24.5)	25 (23.8)
Previous renal transplant(s)	Yes	9 (8.5)	15 (14.2)
Total accumulated time with a functional renal transplant (months) (n=22)	median (IQR)	77 (25-174)	73.5 (4-204)
Spent time on peritoneal dialysis	Yes	13 (12.3)	19 (17.9)
Total accumulated time patient has spent on peritoneal dialysis (months) (n=32)	median (IQR)	11 (4-24)	31 (12-67)

S5 Health-related Quality of Life (HRQoL)

		Paclitaxel-coated balloon (n=106)	Standard balloon (n=106)
Baseline (n=196)			
EQ-5D-5L [Description of health today]			
Mobility	No problems	29 (28.7)	27 (28.4)
	Slight problems	23 (22.8)	27 (28.4)
	Moderate problems	29 (28.7)	20 (21.1)
	Severe problems	13 (12.9)	18 (18.9)
	Unable to walk about	7 (6.9)	3 (3.2)
Self-Care	No problems	68 (67.3)	60 (63.2)
	Slight problems	17 (16.8)	18 (18.9)
	Moderate problems	7 (6.9)	10 (10.5)
	Severe problems	5 (5.0)	5 (5.3)
	Unable to wash/dress myself	4 (4.0)	2 (2.1)
Usual Activities	No problems	28 (27.7)	32 (33.7)
	Slight problems	32 (31.7)	26 (27.4)
	Moderate problems	22 (21.7)	22 (23.2)
	Severe problems	10 (9.9)	10 (10.5)
	Unable to do usual activities	9 (8.9)	5 (5.3)
Pain/Discomfort	None	44 (43.6)	27 (28.4)
	Slight	28 (27.7)	31 (32.6)
	Moderate	18 (17.8)	29 (30.5)
	Severe	7 (6.9)	7 (7.4)
	Extreme	4 (4.0)	1 (1.1)
Anxiety/Depression	None	66 (65.3)	47 (49.5)
	Slight	20 (19.8)	29 (30.5)
	Moderate	12 (11.9)	17 (17.9)
	Severe	1 (1.0)	2 (2.1)
	Extreme	2 (2.0)	-
Health today (VAS) (0=worst imaginable; 100=best imaginable)	mean (SD)	66.3 (19.4) n=99	63.6 (22.3) n=95
POS-S Renal [How have each of the 17 symptoms affected them and how they have felt over past week] (n=191)			
Total score (0=not at all; 4=overwhelmingly) Min=0 Max=68	mean (SD)	12.9 (9.3) n=97	13.7 (9.4) n=94

EQ-5D-5L post randomisation			
6-months (n=145)			
Mobility	No problems	17 (24.3)	19 (25.3)
	Slight problems	21 (30.0)	19 (25.3)
	Moderate problems	11 (15.7)	19 (25.3)
	Severe problems	14 (20.0)	12 (16.0)
	Unable to walk about	7 (10.0)	6 (8.0)
Self-Care	No problems	44 (62.9)	42 (56.0)
	Slight problems	10 (14.3)	13 (17.3)
	Moderate problems	5 (7.1)	11 (14.7)
	Severe problems	8 (11.4)	7 (9.3)
	Unable to wash/dress myself	3 (4.3)	2 (2.7)
Usual Activities	No problems	26 (37.1)	24 (32.0)
	Slight problems	15 (21.4)	24 (32.0)
	Moderate problems	11 (15.7)	12 (16.0)
	Severe problems	11 (15.7)	11 (14.7)
	Unable to do usual activities	7 (10.0)	4 (5.3)
Pain/Discomfort	None	28 (40.0)	15 (20.3)
	Slight	18 (25.7)	25 (33.8)
	Moderate	14 (20.0)	22 (29.7)
	Severe	8 (11.4)	10 (13.5)
	Extreme	2 (2.9)	2 (2.7)
Anxiety/Depression	None	40 (57.1)	36 (48.0)
	Slight	16 (22.9)	31 (41.3)
	Moderate	10 (14.3)	6 (8.0)
	Severe	3 (4.3)	2 (2.7)
	Extreme	1 (1.4)	-
12-months (n=95)			
Mobility	No problems	17 (35.4)	9 (19.1)
	Slight problems	10 (20.8)	16 (34.0)
	Moderate problems	9 (18.8)	13 (27.7)
	Severe problems	7 (14.6)	8 (17.0)
	Unable to walk about	5 (10.4)	1 (2.1)
Self-Care	No problems	31 (64.6)	28 (59.6)
	Slight problems	10 (20.8)	12 (25.5)
	Moderate problems	2 (4.2)	6 (12.8)
	Severe problems	3 (6.3)	1 (2.1)
	Unable to wash/dress myself	2 (4.2)	-
Usual Activities	No problems	17 (35.4)	13 (27.7)
	Slight problems	15 (31.3)	13 (27.7)

	Moderate problems	5 (10.4)	14 (29.8)
	Severe problems	4 (8.3)	6 (12.8)
	Unable to do usual activities	7 (14.6)	1 (2.1)
Pain/Discomfort	None	20 (41.7)	15 (31.9)
	Slight	12 (25.0)	15 (31.9)
	Moderate	10 (20.8)	11 (23.4)
	Severe	3 (6.3)	5 (10.6)
	Extreme	3 (6.3)	1 (2.1)
Anxiety/Depression	None	28 (58.3)	24 (51.1)
	Slight	12 (25.0)	19 (40.4)
	Moderate	6 (12.5)	4 (8.5)
	Severe	-	-
	Extreme	2 (4.2)	-

Data are presented as *n* (%) unless otherwise specified; VAS: visual analogue scale

S6 List of adverse events

Treatment group	Adverse event category	Serious Adverse Event	Intensity
Paclitaxel-coated balloon	Insertion of CVC	0. No	1. Mild
Paclitaxel-coated balloon	Insertion of CVC	0. No	1. Mild
Paclitaxel-coated balloon	Insertion of CVC	0. No	1. Mild
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	0. No	2. Moderate
Paclitaxel-coated balloon	Insertion of CVC	1. Yes	2. Moderate
Paclitaxel-coated balloon	Thrombosed access	0. No	1. Mild
Paclitaxel-coated balloon	Thrombosed access	1. Yes	1. Mild
Paclitaxel-coated balloon	Thrombosed access	1. Yes	1. Mild
Paclitaxel-coated balloon	Thrombosed access	1. Yes	2. Moderate
Paclitaxel-coated balloon	Thrombosed access	1. Yes	2. Moderate
Paclitaxel-coated balloon	Thrombosed access	1. Yes	2. Moderate
Paclitaxel-coated balloon	Access-related (other)	0. No	1. Mild
Paclitaxel-coated balloon	Access-related (other)	0. No	1. Mild
Paclitaxel-coated balloon	Access-related (other)	0. No	1. Mild
Paclitaxel-coated balloon	Access-related (other)	0. No	1. Mild
Paclitaxel-coated balloon	Access-related (other)	0. No	1. Mild
Paclitaxel-coated balloon	Access-related (other)	0. No	1. Mild
Paclitaxel-coated balloon	Access-related (other)	0. No	1. Mild
Paclitaxel-coated balloon	Access-related (other)	0. No	2. Moderate
Paclitaxel-coated balloon	Access-related (other)	0. No	2. Moderate
Paclitaxel-coated balloon	Access-related (other)	0. No	3. Severe
Paclitaxel-coated balloon	Access-related (other)	0. No	3. Severe
Paclitaxel-coated balloon	Access-related (other)	1. Yes	1. Mild
Paclitaxel-coated balloon	Access-related (other)	1. Yes	1. Mild
Paclitaxel-coated balloon	Access-related (other)	1. Yes	2. Moderate
Paclitaxel-coated balloon	Access-related (other)	1. Yes	2. Moderate
Paclitaxel-coated balloon	Access-related (other)	1. Yes	3. Severe
Paclitaxel-coated balloon	Access-related (other)	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	0. No	1. Mild
Paclitaxel-coated balloon	Cardiovascular/respiratory	0. No	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	1. Mild
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	1. Mild

Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	1. Mild
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	1. Mild
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	1. Mild
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Cardiovascular/respiratory	1. Yes	3. Severe
Paclitaxel-coated balloon	Gastrointestinal	1. Yes	3. Severe
Paclitaxel-coated balloon	Foot disease	1. Yes	2. Moderate
Paclitaxel-coated balloon	Foot disease	1. Yes	3. Severe
Paclitaxel-coated balloon	Foot disease	1. Yes	3. Severe
Paclitaxel-coated balloon	Fall/syncope	1. Yes	1. Mild
Paclitaxel-coated balloon	Fall/syncope	1. Yes	2. Moderate
Paclitaxel-coated balloon	Fall/syncope	1. Yes	2. Moderate
Paclitaxel-coated balloon	Fall/syncope	1. Yes	2. Moderate
Paclitaxel-coated balloon	Musculoskeletal	1. Yes	2. Moderate
Paclitaxel-coated balloon	Musculoskeletal	1. Yes	2. Moderate
Paclitaxel-coated balloon	Musculoskeletal	1. Yes	3. Severe
Paclitaxel-coated balloon	Hypertension	1. Yes	3. Severe
Paclitaxel-coated balloon	Bacteraemia	1. Yes	2. Moderate
Paclitaxel-coated balloon	Bacteraemia	1. Yes	2. Moderate
Paclitaxel-coated balloon	Cutaneous	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	0. No	1. Mild
Paclitaxel-coated balloon	Other	0. No	1. Mild
Paclitaxel-coated balloon	Other	0. No	1. Mild
Paclitaxel-coated balloon	Other	0. No	1. Mild
Paclitaxel-coated balloon	Other	0. No	3. Severe
Paclitaxel-coated balloon	Other	1. Yes	1. Mild
Paclitaxel-coated balloon	Other	1. Yes	1. Mild
Paclitaxel-coated balloon	Other	1. Yes	1. Mild

Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Other	1. Yes	2. Moderate
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Paclitaxel-coated balloon	Death	1. Yes	3. Severe
Standard balloon	Insertion of CVC	0. No	1. Mild
Standard balloon	Insertion of CVC	0. No	1. Mild
Standard balloon	Insertion of CVC	0. No	1. Mild
Standard balloon	Insertion of CVC	0. No	1. Mild
Standard balloon	Insertion of CVC	0. No	1. Mild
Standard balloon	Insertion of CVC	0. No	2. Moderate
Standard balloon	Insertion of CVC	0. No	2. Moderate
Standard balloon	Insertion of CVC	0. No	2. Moderate
Standard balloon	Insertion of CVC	1. Yes	1. Mild
Standard balloon	Thrombosed access	0. No	2. Moderate
Standard balloon	Thrombosed access	1. Yes	1. Mild
Standard balloon	Thrombosed access	1. Yes	2. Moderate
Standard balloon	Thrombosed access	1. Yes	2. Moderate
Standard balloon	Thrombosed access	1. Yes	3. Severe
Standard balloon	Access-related (other)	0. No	1. Mild
Standard balloon	Access-related (other)	0. No	1. Mild
Standard balloon	Access-related (other)	0. No	1. Mild

Section S7 Protocols and statistical analysis plans:

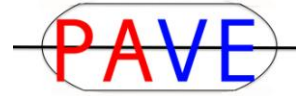
Original protocol (version 2.0, approved before the first site opened)

Final protocol (version 9.0)

Version control document (summary of changes)

Original statistical analysis plan (version 1.0)

Second and final statistical analysis plan (version 2.0, changes listed in section 1.6)



PROTOCOL TITLE

Paclitaxel assisted balloon Angioplasty of Venous stenosis in haEmodialysis access (PAVE); A double-blind randomised controlled clinical trial to determine the efficacy of paclitaxel-assisted balloon angioplasty of venous stenoses in haemodialysis access

Trial Identifiers ISRCTN – REC Number – 15/LO/0638

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1. Introduction

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- 1.2 Risks and benefits
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Study Synopsis

Title	Paclitaxel assisted balloon Angioplasty of Venous stenosis in haEmodialysis access.
Protocol Short Title	PAVE Trial
Protocol Version number/ Date	Version 1.0
Is the study a Pilot?	No
Study Hypothesis	The hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic arteriovenous fistulae.
Methodology	Double-blind multicentre randomised controlled trial
Sponsor name	King's College London / GSTT NHS Foundation Trust
Chief Investigator	Dr Michael Robson
REC number	15/LO/0638
Condition under investigation	Arteriovenous fistulae used for haemodialysis in patients with end stage kidney disease.
Purpose of clinical trial	RCT to assess the efficacy of additional paclitaxel-coated balloon fistuloplasty compared to plain balloon fistuloplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.
Number of Patients	211
Trial Design	Double-blind multicentre randomised controlled trial with variable follow up (minimum 1 year)
Endpoints	<p>The primary endpoint is time to end of target lesion primary patency (TLPP). Secondary endpoints:</p> <ol style="list-style-type: none"> 1. Angiographically determined late lumen loss 2. The rate of binary angiographic re-stenosis 3. Time to end of access circuit primary patency 4. Time to end of access circuit cumulative patency 5. Procedural success 6. Number of thrombosis events 7. Adverse events 8. Patient quality of life assessed by EQ-5D and POS-S Renal
Inclusion Criteria	<ol style="list-style-type: none"> 1. Patients (18 years or over) who have a native AVF in the arm that has been used for haemodialysis for at least 12 dialysis sessions 2. An indication for a fistuloplasty as determined by the local clinical team 3. The access circuit is free of synthetic graft material or stents 4. A reduction of vessel diameter of $\geq 50\%$ measured angiographically, and a reference diameter of the outflow vein of at least 4 mm and less than the size of the largest available drug-coated balloon 5. A residual stenosis of $\leq 30\%$ after plain balloon fistuloplasty
Exclusion Criteria	<ol style="list-style-type: none"> 1. Patient unable to give informed consent 2. Patient unwilling or unable to comply with all study-related procedures 3. Systemic or local (to the fistula) infection treated for less than 10 days prior to the study procedure 4. Synchronous venous lesion (with a reduction of vessel diameter of $\geq 50\%$ measured angiographically) in the same access circuit 5. Location of stenosis beyond the thoracic inlet 6. Thrombosed (failed) dialysis circuit at time of treatment 7. Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children within two years of study treatment 8. Known hypersensitivity or contraindication to contrast medium which cannot be adequately premedicated 9. Known hypersensitivity or contraindication to paclitaxel
Statistical Methodology and Analysis	To test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival we will use Cox-Proportional Hazards regression, on an intention to treat basis.



Device Name	Lutonix 035 Drug Coated Balloon PTA Catheter (Treatment) Ultraverse 035 PTA Dilatation Catheter (Placebo) Dorado PTA Dilatation Catheter (Plain balloon)
Manufacturer Name	C.R Bard, Inc.
Principle intended use	Angioplasty of stenosed blood vessels
Is the device CE-marked and used within its purpose?	Yes
Is the device currently used within the department?	Yes

Description and Maintenance and storage of device

The balloons will be stored under routine conditions in the radiology department.
 No special measures or maintenance is needed.

Are the devices registered on the DoH MIA Master Indemnity Scheme?	Yes
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Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
Atm	Atmospheres (pressure)
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
ISRCTN	International Standard Randomised Controlled Trial Number
REC	Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TLPP	Target Lesion primary patency
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Introduction

1.1. Existing research

Vascular access for haemodialysis

The 2012 UK Renal Registry report (www.renalreg.com) found that 43.9% of patients with end-stage kidney disease in the UK are on haemodialysis. This equated to 365 patients per million population in the UK in 2011. This number has increased every year with an overall increase of 3.6% from 2006 to 2011. In order to perform haemodialysis, reliable vascular access is essential. It is universally agreed that the optimal form of access is a native arteriovenous fistula (AVF). Although these are superior to synthetic arteriovenous grafts (AVGs), both AVFs and AVGs have a limited lifespan. Data from the Dialysis Outcomes and Practice Study (DOPPS) showed that in the US the one year patency for AVFs and AVGs is 68% and 49% respectively [1]. In Europe, one-year AVF survival was somewhat better at 83% but there is still a need for improvement.

Problems with vascular access are an important cause of morbidity and mortality in haemodialysis patients. In the US, it has been estimated that \$1bn per year is spent on vascular access and its complications [2]. A recent survey in the UK found that haemodialysis patients occupy 320,000 bed days per year, with 30% of admissions related to vascular access (Renal Association vascular access audit, available at www.renal.org). Haemodialysis patients are at a greatly increased risk of invasive MRSA infection and this is largely related to the use of central venous catheters instead of AVFs or AVGs. When thrombosis or stenosis occurs in an AVF or AVG, a central venous catheter may be used for several months until an AVF or AVG is formed and is usable. In some patients, a central venous catheter may become the only dialysis access that can be used. Data from the US showed that the risk of invasive infection is increased 100 fold over the general population in haemodialysis patients, with 85% having catheters of invasive devices, and 90% requiring hospitalisation with a 17% mortality [3]. It is therefore imperative to preserve each AVF or AVG for as long as possible and to avoid the use of central venous catheters which lead to infective complications.

The initial therapy for a stenosis in an AVF is radiological balloon dilatation or angioplasty. Monitoring of AVFs for reduced blood flow and pre-emptive angioplasty, or surgery, is performed in some centres. Limited evidence supports this approach [4-6]. In contrast, the need for intervention when AVFs are clinically dysfunctional, with angioplasty or surgery, is established and will improve fistula function. A major concern however is the longevity of this effect. One recent study addressed this and documented the outcomes after angioplasty in 159 AVFs. Angioplasty was performed due to AVF dysfunction in 96% of cases. Primary assisted patency (AVF working regardless of repeat intervention) was 89% and 85% at 6 and 12 months respectively. However at 6, 12 and 24 months, the primary unassisted patency (AVF working with no repeat intervention) was 61%, 42% and 35% respectively [7]. These results are similar to our own local audit data, which showed 53% and 33% primary unassisted patency rate at 6 and 12 months respectively. It is also similar, as regards event rate, to the prospective study of Tessitore et al (5). In this study the primary outcome was AVF patency following angioplasty regardless of repeat intervention. However, the restenosis rate following the initial angioplasty was reported to be 39% per year, with a median time to this event of 8 months. In addition to the need for better interventions to reduce restenosis rates, there is also a need to better understand and identify the different types of response that occur following intervention.

The biology of arteriovenous fistula dysfunction

Neointimal hyperplasia leads to stenoses in the venous segments of AVFs, with the pathology characterised by an expansion of alpha smooth muscle actin positive myofibroblasts in the neointima [8]. In arteries, the contribution of bone-marrow derived cells to tissue repair depends on the nature and severity of injury [9]. The contribution of bone marrow cells to venous neointimal hyperplasia is not resolved and the data from animal studies are conflicting. Two studies using bone marrow transplantation with cells containing a green fluorescent protein (GFP) or β -galactosidase reporter gene, have suggested a minimal contribution of bone-marrow derived cells in mouse and rat model respectively [10, 11]. However a further study employing a murine vein graft, has suggested that at least 20% of neointimal cells may be bone marrow derived [12]. GFP positive cells were detected by a more sensitive PCR method and these technical differences were suggested as a reason for discrepancies with other studies.

In addition to these conflicting data on the origin of neointimal cells, it should be noted that none of the previous reports induced vein injury in way that would mirror the changes induced by angioplasty. Instead, most have focussed on the development of primary stenosis in venous grafts undergoing arterialisation, in which endothelium is 'traumatised' or activated by changes in the flow characteristics of arterial blood to which it becomes exposed. Given the data from arterial studies, a contribution from bone marrow cells to the alpha smooth muscle actin producing cells in the hyperplastic neointima of a dysfunctional AV fistula is highly likely with the degree of trauma to the endothelium that would follow angioplasty. Angioplasty causes vessel wall damage with rupture of the junction between the intima and the media, with a burst of proliferation and repair. Much of our understanding of aggressive neointimal formation in this context comes from arterial studies [13], but similar pathology and an increase in proliferation has been shown in AVFs following venous angioplasty [14].

Paclitaxel exerts an antiproliferative effect by interfering with cell microtubule function [15]. Systemic administration of paclitaxel after angioplasty in the rat carotid artery showed that a significant reduction in neointimal proliferation could be achieved at doses much lower than antineoplastic levels [16]. In rat and human cultured cell models, paclitaxel inhibited vascular smooth muscle cell migration and proliferation [16, 17], consistent with its effects in vivo. As an alternative to systemic therapy, local drug delivery offers the advantages of allowing high local concentrations of drug at the treatment site while minimising systemic toxic effects. Proof of this possibility was initially shown using paclitaxel-coated stents in pig coronary arteries [18].

Recent advances in technology have allowed angioplasty balloons to be coated with paclitaxel. This allows local delivery of paclitaxel to the site of stenosis. A number of multi-centre randomised controlled trials in the coronary and peripheral arterial circulation have established the positive benefit of drug-coated balloons [19, 20]. A small pilot study has suggested efficacy in dialysis patients [21]. In this study, 40 patients with AVFs or AVGs were randomised to paclitaxel for the treatment of a clinically important stenosis. Unassisted primary patency of the treated lesion (defined angiographically as a binary readout of <50% stenosis) at 6 months was significantly better in the paclitaxel-coated balloon group (70 v 25%). This study may be criticised on a number of points. These include the use of an angiographic rather than a clinical endpoint, the lack of blinding and independent angiographic core lab analysis, the very small sample size originally intended to test non-inferiority only (with a wide 15% non-inferiority limit), and the short 6-month follow-up. In addition, a range of balloons was used in the control group for post-dilation after the paclitaxel-coated balloons, and these were not universally high pressure and non-compliant. This may have added variability to the outcome. Furthermore, the inclusion of both AVFs (35%) and AVGs (65%) may have resulted in significant confounding, given the difference in survival rates associated to the two types of access. Despite these

limitations, the results suggested that a further study of efficacy was warranted, which is what we propose here. This is the first large scale randomised controlled trial designed to test superiority of drug-coated balloons in haemodialysis access circuits.

1.2. Risks and benefits

The risks for patients taking part in this study are minimal. The plain balloon fistuloplasty is standard of care and the additional intervention will be the use of a paclitaxel-coated balloon or control balloon following this initial dilatation. The paclitaxel-coated balloons that will be used are CE marked and there have been no safety concerns with their use. In the specific context of haemodialysis AVFs, the pilot study performed did not raise any safety concerns [21].

1.3. Rationale for current study:

The overriding aim of this study is preservation of vascular access for haemodialysis with a reduction in restenosis and the need for repeat fistuloplasties.

Clinical Trial

Our hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic AVFs. As detailed in section 1.1, this hypothesis is supported by what is known of the effects of paclitaxel on the biology of neointimal formation, results in trials involving coronary and peripheral arteries, and a pilot study vascular access for haemodialysis.

This need for repeat procedures following angioplasty is expensive and inconvenient for patients and is needed in around 60% of patients during the first year [7]. As detailed in our sample size calculation we predict that the use of paclitaxel coated balloons will lead to an avoidance of the need for repeat angioplasty. Repeat angioplasties will also have a negative effect on patient quality of life and a reduction in these will be a benefit in addition to the reduction in cost.

Collection of patient samples

This clinical trial offers a unique opportunity to collect patient samples alongside detailed and carefully collected clinical and angiographic data in the setting of a clinical trial. This will form an important resource for future laboratory based studies on biomarkers and AVF outcomes.

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2. Trial Objectives, Design and Statistics

2.1. Trial objectives

The purpose of this RCT is to assess the efficacy of additional paclitaxel-coated balloon fistuloplasty compared to plain balloon fistuloplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.

Primary Endpoint:

Time to end of target lesion primary patency

This is defined as patency with no re-intervention to the area 5mm proximal within, and 5 mm distal to, the index treatment segment. Target lesion primary patency ends when *any* of the following occur: (a) re-intervention to the treatment segment; (b) thrombotic occlusion that includes the treatment segment; (c) surgical intervention that excludes the treatment segment from the access circuit; (d) abandonment of the AVF due to an inability to retreat the treatment segment.

Referral for a repeat procedure will originate from the clinical team who are unaware of whether the patient received treatment with a paclitaxel-coated balloon or uncoated control balloon.

In order to confirm there is a significant stenosis prior to fistulography, a duplex ultrasound is encouraged but is not mandatory.

A different radiologist to the one performing the index procedure will perform repeat procedures when possible but it is not possible to guarantee this. Therefore the radiologist performing the repeat procedure may have knowledge of whether the patient was treated with drug-coated balloon or placebo.

In order to allow us to demonstrate that there is no bias in the final decision to proceed with the repeat intervention we will do the following: In patients *who have not yet reached the primary endpoint*, any pre-procedure fistulograms prior to re-intervention or potential re-intervention will be sent to an independent angiographic laboratory for analysis. This will allow confirmation that a significant stenosis was found in all patients who received a repeat intervention, and not in the small number who underwent fistulography but not an intervention, regardless of which arm of the trial the patient is in. The specifications for this fistulogram are defined in section 4.5.

Secondary Endpoints:

1. Angiographically determined late lumen loss.

This is the difference between the diameter of the treatment segment post-procedure and the diameter at 6 months as measured by an independent core laboratory. If a patient has a repeat procedure to the treatment segment before 6 months, then the pre-intervention images will be used for analysis and a fistulogram at 6 months will not be performed.

2. The rate of angiographic binary re-stenosis.

This is defined as the incidence of stenosis of at least 50% within the treated lesion at the 6 month follow-up fistulogram. If a patient has a repeat procedure to the index lesion before 6 months, then the pre-intervention images will be used for analysis and a fistulogram at 6 months will not be performed.



3. Time to end of access circuit primary patency

The access circuit is defined as starting at the arterial anastomosis and ending at the cavoatrial junction. Access circuit primary patency ends when *any* of the following occur: (a) access circuit thrombosis, (b) an intervention (either radiological or surgical) anywhere in the access circuit, or (c) the access circuit is abandoned due to an inability to treat any lesion.

4. Time to end of access circuit cumulative patency

Access circuit cumulative patency ends when the AVF is abandoned, regardless of radiological or surgical intervention, with or without a thrombosis event. Multiple/repetitive treatments for stenoses that restore patency are compatible with cumulative patency.

5. Procedural success (residual stenosis \leq 30% on completion fistulogram II, see section 4.4 below)
6. Number of thrombosis events
7. Adverse events (e.g. fistula rupture, infection)
8. Patient quality of life as assessed by the EuroQuol EQ-5D generic health survey, and the disease specific Patient (or Palliative care) Outcome Scale symptom score-renal (POS-S Renal) [22].

2.2 Trial design

The study design used to achieve this will be a double-blind multicentre randomised controlled trial. We will recruit 211 patients over a two-year period. Patients will be randomized in a 1:1 ratio. Randomisation will be stratified for two variables. These will be firstly study centre and secondly, whether they have had a previous radiological intervention to the treatment area or not. Patients will be followed up for a minimum of one year, and all patients will continue in the study until the last patient has completed one year of follow up.



2.3 Trial schedule

	Pre-procedure	Procedure	Post-procedure ****												
			Day 1-3	nth 3	nth 6	nth 9	nth 12	nth 15	nth 18	nth 21	nth 24	nth 27	nth 30	nth 33	nth 36
Patient registration and consent	x														
Medical history (including indication for fistuloplasty)	x														
Consideration of eligibility	x														
Discussion and confirmation of potential eligibility with radiologist	x														
Blood samples (taken on dialysis when possible)	x		x	x	x										
Pre-procedure fistulogram *		x													
Plain balloon fistuloplasty			x												
Completion fistulogram I *				x											
Randomisation					x										
Study treatment						x									
Completion fistulogram II							x								
Protocol fistulogram															
Follow up assessments ** ***				x	x	x	x	x	x	x	x	x	x	x	x
Quality of life assessments (POS-S Renal and EQ-5D)	x				x		x								

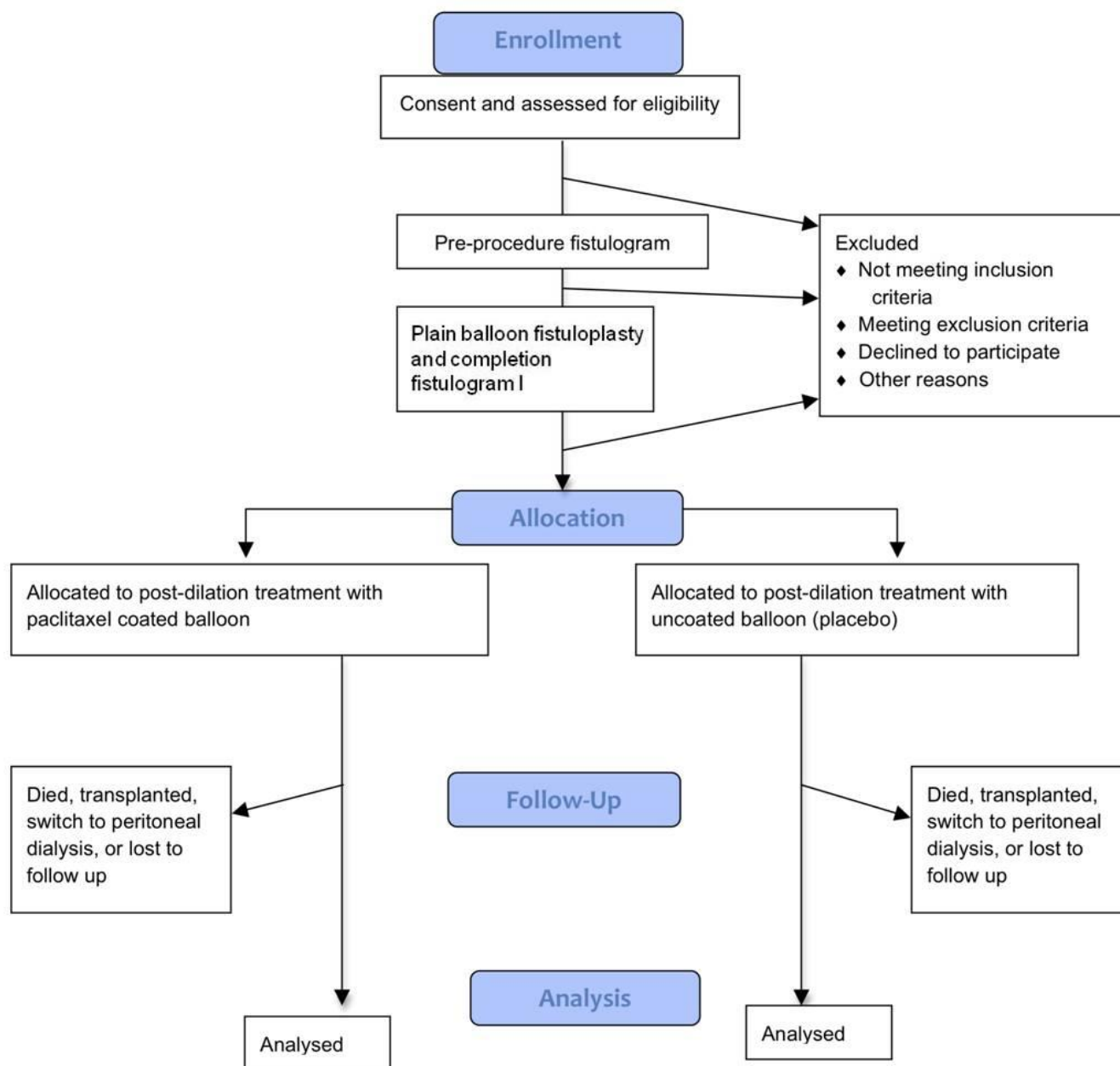
* Prior to randomisation, eligibility will be reviewed based on the radiological findings on both the pre-procedure fistulogram and completion fistulogram I

**At each follow up assessment information to be checked or collected will include the following: target lesion primary patency, access circuit primary and cumulative patency, access circuit interventions, thrombosis events, patient medications, access circuit dysfunction, and adverse events.

***Follow up will be for a minimum of 12 months and a maximum of 36 months.

****Post-procedure study assessments occur every 3 months \pm 1 month.

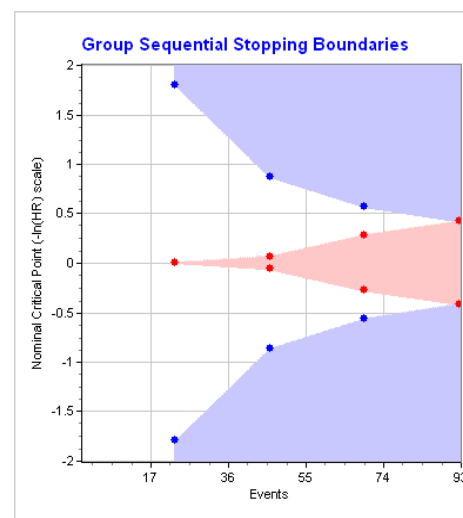
2.4 Trial flowchart



2.5 Trial statistics

Analysis of Primary Outcome: To test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival we will use Cox-Proportional Hazards regression, on an intention to treat basis. Primary analysis will be repeated using multivariate cox regression for the adjustment of the treatment effect size for the effect of known clinical covariates. Patients with TLPP at the end of follow up will be considered censored, as will those who receive a renal transplant, switch to peritoneal dialysis or are lost to follow up before the study end. Kaplan-Meier plots, hazard-ratio and its confidence interval will be used to describe the results.

Analysis of Secondary Outcomes: Effects on secondary outcomes will be analysed using the same strategy for time-to-event variables, and generalized linear models for binary and continuous outcome measures, adjusting for the effects of relevant covariates when appropriate. Continuous variables will be checked for normality, transformed if necessary or otherwise analysed using a Wilcoxon-signed-rank test for independent samples.



Missing Values and Drop-outs: If necessary, multiple imputation will be used for the imputation of missing values in baseline variables and secondary outcomes. Patients lost to follow up will be compared to patients who reach complete follow up in baseline characteristics and adverse events to test whether drop-outs are random.

Interim Analysis: Interim analysis of the primary outcome will be performed three times throughout the study, based on the cumulative number of failures of the treatment area, i.e. after 27, 54 and 81 events, expected approximately at 9, 14 and 19 months of study under the null, and at months 11, 17, and 23 under the alternative. Group sequential stopping boundaries have been calculated using a Lan-de-Mets spending function (with O'Brian-Fleming parameters), to allow early stopping for rejection of the null or the alternative hypotheses. Stopping in case of boundary crossing is non-binding.

3. Sample Size, Selection and Withdrawal of Subjects

3.1 Sample size

For the definition of the survival curve in the placebo balloon group, we assumed target lesion primary patency of 61%, 42%, and 35% at 6, 12 and 24 months respectively. This was consistent with published results [7] and with our own audit data. A hazard ratio (HR) of 0.5 was chosen as the minimum clinically relevant effect size. Katsanos et al. [21] found a HR of 0.3 for TLPP at 6 months; however, the confidence interval was broad and the effect size is expected to be closer to the null when AVGs are excluded. Based on these assumptions, it is expected that the paclitaxel coated balloon group will show 78%, 65%, and 59% survival of TLPP at 6, 12 and 24 months respectively. Recruiting 211 patients, with variable follow up, a minimum follow up of 1 year, and three interim analyses, will provide 94% power to detect a statistically significant difference between the two groups in TLPP survival with 2-sided 5% type I error rate. It is expected that 108 patients will experience fistula failure during the follow up period.



The required sample size has been estimated assuming cumulative 10% drop-out in each treatment arm by the end of the study, and recruitment of 2 patients per month (ppm) during the first three months, 8 ppm up to 7 months, and 12 ppm onwards. The expected accrual duration will be 22 months, and the maximum study duration (including follow-up) 34 months.

3.2 Inclusion criteria

1. Patients (18 years or over) who have a native AVF in the arm that has been used for haemodialysis for at least 12 dialysis sessions.
2. An indication for a fistuloplasty as determined by the local clinical team
3. The access circuit is free of synthetic graft material or stents
4. A reduction of vessel diameter of $\geq 50\%$ measured angiographically, and a reference diameter of the outflow vein of at least 4 mm and less than the size of the largest available drug-coated balloon
5. A residual stenosis $\leq 30\%$ after plain balloon fistuloplasty

3.3 Exclusion criteria

1. Patient unable to give informed consent
2. Patient unwilling or unable to comply with all study-related procedures
3. Systemic or local (to the fistula) infection treated for less than 10 days prior to the study procedure
4. Synchronous venous lesion, with a reduction of vessel diameter of $\geq 50\%$ measured angiographically, in the same access circuit
5. Location of stenosis beyond the thoracic inlet
6. Thrombosed (failed) dialysis circuit at time of treatment
7. Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children, within two years of study treatment
8. Known hypersensitivity or contraindication to contrast medium which cannot be adequately premedicated
9. Known hypersensitivity or contraindication to paclitaxel



3.4 Criteria for premature withdrawal

Participants have the right to withdraw from the study at any time for any reason.

Participants will be withdrawn from the study if any of the following occur:

- Death of participant
- Participant receives a transplant
- Participant is changed from haemodialysis to peritoneal dialysis

The PI also has the right to withdraw patients from the study in the event of inter-current illness, AEs, SAE's, protocol violations, administrative reasons or other reasons, e.g. the participant is no longer being treated at a hospital included in the study.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Participants who wish to withdraw from 'treatment' will be asked to confirm whether they are still willing to provide study specific data and samples for scientific laboratory analysis according to the trial protocol.

4. Study Procedures

4.1 Screening procedures

Patients that may be eligible will be identified in a vascular access clinic and assessed by surgeons, specialist nurses and nephrologists.

In order to confirm there is a significant stenosis prior to angiography, a duplex ultrasound is encouraged but is not mandatory.

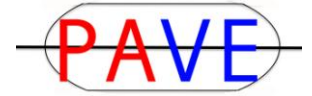
At least 24 hours after being given the patient information sheet and before entering the angiography room for the pre-procedure fistulogram, consent will be taken and eligibility criteria as listed above in section 3 will be assessed. Inclusion criteria 1 and 2 will be confirmed and exclusion criteria 1-3 and 6-9 will be assessed.

The radiologist who will perform the pre-procedure fistulogram will be informed that the patient is potentially eligible for the study.

4.2 The pre-procedure fistulogram

This will be performed in a dedicated Interventional Radiology suite equipped with digital subtraction angiogram, image overlay/roadmap post processing capabilities and ability to capture still and video DICOM file data.

This will be take place immediately prior to the plain balloon fistuloplasty.



It will be performed through a sheath or cannula placed in the dialysis circuit according to the following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second
2. The entire access circuit from anastomosis to central vein covered in up to 3 stages
3. Medial epicondyle of humerus visible bony landmark on lower arm acquisition, acromioclavicular joint on upper arm and central acquisitions
4. Measurement ruler in view
5. Lower arm acquisition to include:
 - i. Anteroposterior Projection of anastomosis
 - ii. Oblique projection of anastomosis (specify oblique and craniocaudal angulation)
6. On the acquisition that best demonstrates the target lesion, the following measurements are made:
 - i. Proximal (close to anastomosis) reference vessel diameter
 - ii. Minimum lumen diameter (MLD)
 - iii. Distal reference vessel diameter

The radiologist will assess inclusion criteria 3 and 4, and exclusion criteria 4 and 5, to decide if the patient remains eligible for the study.

4.3 The plain balloon fistuloplasty procedure

This will be performed in a dedicated Interventional Radiology suite equipped with digital subtraction angiogram, image overlay/roadmap post processing capabilities and ability to capture still and video DICOM file data, according to the following specifications:

Prior to treatment 3000-5000 IU of heparin is administered. For all patients treatment has two components. The first is fistuloplasty, performed with a dedicated high pressure balloon (Bard Dorado) ensuring the following criteria are met:

1. Sized to nominal vein diameter
2. Up to 24 Atm to ensure obliteration of the lesion waist
3. Minimum duration of balloon inflation 1 minute.

If further plain balloon fistuloplasty treatment is required, then this may be administered once more only.



Completion fistulogram I is performed after the plain balloon fistuloplasty to ensure adequate therapy according to the following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second
2. Acquisition that demonstrates the target lesion matched as close as possible to the respective pre-procedure fistulogram acquisition
3. Measurement ruler in view
4. The following measurements are made:
 - i. Proximal (close to anastomosis) reference vessel diameter
 - ii. Minimum lumen diameter (MLD)
 - iii. Distal reference vessel diameter

The radiologist will assess completion fistulogram I and decide if the residual stenosis is $\leq 30\%$ (inclusion criteria 5). If this is the case the patient will proceed to randomisation, but if not the patient will be excluded.

4.4 Randomisation procedures

Randomisation will take place via a web based randomisation service, hosted at the UKCRC registered clinical trials unit at KCL. Site staff will access the service via www.ctu.co.uk using a computer in the angiography room or an office nearby. It will be performed by the radiologist or their nominee. Each randomiser will have unique user access. Access will be provided by the CTU upon the authorisation of the trial manager, once the delegation of authority form has been completed and relevant documentation regarding the individuals has been collected. Nominees must not be clinicians or nurses who may decide to refer the patient for re-intervention.

Patients will be randomized in a 1:1 ratio. The two groups will be stratified by two variables. These will be firstly study centre and secondly, whether they have had a previous radiological intervention to the treatment area or not. Once randomised, email confirmations will be generated from the randomisation system and will be sent to relevant study staff in a blinded or unblinded format, depending on their role in the study.

If it is not possible to use the randomisation system randomisation may occur using the toss of a coin in order to avoid losing the patient from the study. *This should only be needed, if at all, in specific and rare situations such as the CTU server being inaccessible.* This will be performed by two people with heads denoting drug-coated balloon, and tails denoting placebo. The CTU must be informed of the coin randomisation as soon as possible.

4.5 Study treatment

In the intervention arm, the second component is insertion of a drug coated balloon (*Bard Lutonix*) of identical diameter and length to the high pressure balloon inflated to nominal pressure at the lesion location for a minimum of 1 minute duration.

Instructions for use of the drug coated balloon are stringently adhered to ensure appropriate preparation and handling of the device.

In the control arm, an identical procedure is followed, but using a placebo balloon that is not drug coated (*Bard Ultraverse*), of identical diameter and length to the high pressure balloon inflated to nominal pressure at the lesion location for a minimum of 1 minute duration.

In both arms, image overlay/roadmap will be utilized to ensure that there is no geographical mismatch between the segments treated with the high and low pressure balloons.



Only the above 3 balloon types (*Bard Dorado, Bard Lutonix and Bard Ultraverse*) may be used in the study to ensure consistency and the above fistuloplasty procedure must be exactly followed.

A completion fistulogram is again performed (completion fistulogram II) to confirm no angiographically visible effect after treatment with the drug-coated or placebo balloon, according to the following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second
2. Acquisition that demonstrates the target lesion matched as close as possible to the respective pre-procedure fistulogram acquisition
3. Measurement ruler in view
4. The following measurements are made:
 - i. Proximal (close to anastomosis) reference vessel diameter
 - ii. Minimum lumen diameter (MLD)
 - iii. Distal reference vessel diameter

Procedural success is defined as a residual stenosis $\leq 30\%$ on completion fistulogram II.

The data file(s) containing the initial pre-procedure fistulogram, and completion fistulogram I and II will be sent to the lead study site with the patient's name replaced by the trial ID, and with each of the above groups of images clearly identified. Completion fistulogram II will then be sent to the independent angiographic laboratory for analysis.

4.6 Study assessments

These will occur every 3 months \pm 1 month. Follow up will be variable but for a minimum of 1 year and a maximum of 3 years. These will involve a clinical assessment to take place either face-to-face or via a telephone conversation. Any face-to-face meetings will usually coincide with dialysis to avoid additional patient travel.

Data recorded for each study assessment will include the following: target lesion primary patency, access circuit primary and cumulative patency, access circuit interventions, thrombosis events, patient medications, access circuit dysfunction, and adverse events. At the 6 month study assessment, the trial team will check if referral for re-intervention is being considered based on clinical concerns. If this is the case then a fistulogram \pm plasty will be performed according to usual clinical practice and the patient will not undergo a protocol fistulogram.

If there are no clinical concerns related to the fistula, then patients will be invited to undergo a protocol fistulogram. Confirmation that there is no contraindication to this protocol fistulogram will be obtained from an appropriate doctor and documented.

4.7 Radiology Assessments

4.7.1 The 6 month protocol fistulogram

This will take place within 2 weeks of the 6 month study assessment.

If a patient has required a repeat fistuloplasty to the treatment area at or before 6 months then they will not undergo the 6 month protocol fistulogram.



All other patients will be invited to undergo a protocol fistulogram 6 months after the index procedure to acquire the data for the angiographic secondary endpoints 1 and 2 above. If a patient declines the 6 month protocol fistulogram or does not have it for another reason, this will not be considered a protocol violation and the patient may continue in the study.

The 6 month protocol fistulogram *must* be performed by a radiologist other than the one who performed the index procedure to ensure that they are blind to which trial arm the participant belongs. With forward planning this should be possible but if it is not then the protocol fistulogram should not be performed.

A fistuloplasty will not be performed at the time of the 6 month protocol fistulogram unless an unsuspected stenosis is found and the radiologist believes that it would be unethical not to intervene. This will not be considered a protocol violation and a fistula intervention form must be completed.

The 6 month protocol fistulogram will be performed in a dedicated Interventional Radiology suite equipped with digital subtraction angiogram, image overlay/roadmap post processing capabilities and ability to capture still and video DICOM file data. It will be performed through a sheath or cannula placed in the dialysis circuit according to the following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second
2. The entire access circuit from anastomosis to central veins covered in up to 3 stages
3. Medial epicondyle of humerus visible bony landmark on lower arm acquisition, acromioclavicular joint on upper arm and central acquisitions
4. Measurement ruler in view
5. Lower arm acquisition to include:
 - i. Anteroposterior Projection of anastomosis
 - ii. Oblique projection of anastomosis (specify oblique and craniocaudal angulation)
6. On the acquisition that best demonstrates the target lesion, the following measurements are made:
 - i. Proximal (close to anastomosis) reference vessel diameter
 - ii. Minimum lumen diameter (MLD)
 - iii. Distal reference vessel diameter

The 6 month protocol fistulogram will be considered to be exclusively trial data. The result of the 6 month protocol fistulogram will not be made available (verbally or in writing) to the clinical team responsible for considering future referral of the patient to radiology. The images will also not be available on the local radiology system. The images will be sent to the lead site in order to be forwarded to the independent core laboratory with the patient's name replaced by the trial ID.



4.7.2 Fistulograms performed for a clinical indication

The follow applies only in patients who have not yet reached the primary endpoint of the trial.

Pre-procedure fistulograms performed for a clinical indication will follow these specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second
2. The entire access circuit from anastomosis to central veins covered in up to 3 stages
3. Medial epicondyle of humerus visible bony landmark on lower arm acquisition, acromioclavicular joint on upper arm and central acquisitions
4. Measurement ruler in view
5. Lower arm acquisition to include:
 - i. Anteroposterior Projection of anastomosis
 - ii. Oblique projection of anastomosis (specify oblique and craniocaudal angulation)
6. On the acquisition that best demonstrates the target lesion, the following measurements are made:
 - i. Proximal (close to anastomosis) reference vessel diameter
 - ii. Minimum lumen diameter (MLD)
 - iii. Distal reference vessel diameter

The image file will be sent to the lead site in order to be forwarded to the independent core laboratory for analysis with the patient details replaced by the trial PIN. This will be sent regardless of whether the fistulogram is followed by a fistuloplasty.

This will allow us to demonstrate that there is no bias in the final decision to proceed, or not, with the repeat intervention.

4.8 End of Study Definition

The clinical trial will end when 211 patients have been recruited and all patients have completed at least one year of follow up.

The trial may be prematurely discontinued by the Sponsor, Funder, Chief Investigator or TSC on the basis of new safety information or for other reasons given by the DMC, TSC, REC, or from other sources. The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the TSC who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected.

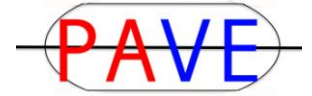
5. Laboratories

5.1 Laboratory tests

There are no local laboratory tests that are required to provide data that directly relate to trial endpoints. A 10 ml blood sample will be requested at the four timepoints stated in the trial schedule (2.3), and is to be sent to the local clinical laboratory for a full blood count and to check the C-reactive protein level. If patients decline some or all of these samples it will not be considered a protocol violation.

5.2 Core laboratory angiographic analysis

The completion fistulogram II (taken after treatment with the drug coated balloon or placebo low pressure balloon) will be analysed in a core laboratory and compared with the pre-procedure



fistulogram performed routinely at 6 months (or the pre-procedure fistulogram taken prior to any re-intervention at the treatment area if this is before 6 months).

In addition, any pre-procedure fistulograms that are not followed by a re-intervention, and any pre-procedure fistulograms that are performed after 6 months and are followed by a re-intervention, will be sent to the core laboratory for analysis. This is to allow an objective assessment of the decision to intervene or not after the pre-procedure fistulogram.

5.3 Research sample Collection

Blood (up to 90 ml) may be taken at each of the time points in the table of events in 2.3. These will be sent to the research laboratory of the CI where the blood will be separated. Research blood samples should not be taken from patients who are known to be hepatitis B sAg, hepatitis C IgG or RNA, or HIV positive.

DNA and RNA will be stored. Cells will be stored in aliquots in liquid nitrogen until thawed for analysis. Serum and/or plasma samples will be stored at -20°C or -80°C until thawed for analysis. Transport, separation and storage will be according to Standard Operating Procedures.

It will not be considered a protocol violation if any of the blood samples are not taken, or are taken at different time points to those specified and patients may continue on the study.

6. Assessment of Safety

We have been informed by the MHRA that the PAVE protocol does not fall within the Clinical Trial Regulations and therefore is not a drug trial. In addition, the drug-coated balloon is a CE-marked medical device, so prior regulatory approval from the MHRA is not needed.

Safety reporting will be in keeping with the requirements for research other than Clinical Trials of Investigational Medicinal Products.

A Serious Adverse Event (SAE) is an untoward occurrence that:

- a) results in death
- b) is life-threatening
- c) requires non-elective hospitalisation or prolongation of existing hospitalisation
- d) results in persistent or significant disability or incapacity
- e) consists of a congenital anomaly or birth defect
- f) is otherwise considered medically significant by the investigator.

All SAEs will be reported by the local investigators on the SAE form to the Chief Investigator, immediately they become aware and within 24 hours at most. A planned or non-elective hospital admission does not need to be reported as an SAE unless the PI decides it should be.

Although it is not an SAE, any pregnancy or fathering of children that occurs within 2 years of the study treatment will be reported via the SAE system as below.

Reports of SAEs will be reviewed by the CI within 24 hours to assess whether the event is related to the research procedure and unexpected (a SUSAR) and if so, it will be onward reported to the REC and DMC within 15 days, in the format prescribed by NRES and published on the website.



Since the study treatment is local and not systemic, non-serious adverse events will be defined as events that the PI considers are directly related to the vascular access that has been treated. These should be recorded throughout the trial and will be captured in the eCRF at each study assessment.

7. Data Monitoring Committee

The membership will be decided by the CI and approved by the NIHR. The DMC includes a statistician and two other independent experts. They will receive a report of recruitment, serious and non-serious adverse events and a summary of accumulated clinical data from the trial statistician, and will meet in person or by telephone. They will report to the TSC who will usually meet in the two weeks following the DMC meeting. The DMC will meet at least annually during the study, approximately 2 weeks prior to the TSC. Additional meetings may take place at the time of interim analysis or in case of recruitment issues. The DMC is advisory to the TSC. The DMC charter will be drafted and agreed prior to recruitment. The Trial Statistician will prepare reports to the DMC.

8. Trial Steering Committee

The TSC will be convened in the post-award period. The membership will be decided by the CI and approved by the NIHR. The chair will be an independent expert. Members will include the CI, a patient representative, and two other independent experts. The TSC will meet at least annually during the study, approximately 2 weeks after the DMC. Additional meetings may take place at the time of interim analysis or in case of recruitment issues. The TSC is an executive committee. Terms of reference of the TSC will be agreed and documented prior to start of recruitment. The Trial Manager will prepare reports to the TSC.

9. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework.

This protocol and related documents will be submitted for review to the London-Chelsea Research Ethics Committee (REC).

The Chief Investigator will submit a final report at conclusion of the trial to the sponsor and the REC.

Annual progress reports will be submitted to the main REC for the study.

10. Data Handling

All samples will be anonymised before laboratory analysis. No patient-related data will be held in research laboratories.

During the study, any paper documents will be held in a locked filing cabinet in a locked office and retained for a minimum of 5 years following the end of the study.



Clinical and research data for the study will be stored on the eCRF system, hosted at the King's Clinical Trials Unit, KCL. The eCRF (InferMed MACRO) is GCP and FDA 21 CFR Part 11 compliant. Data entry staff at site will be provided with unique usernames and passwords to the system and will be trained in data entry by the trial manager. The trial manager will visit sites to review data on the system, raise discrepancies and confirm source data verification checks. All requests for access to the data entry system must be authorised by the trial manager. All requests for data exports must be authorised by the trial statistician. The trial manager will work with the CI and the trial statistician to ensure data is checked and cleaned on an ongoing basis and will confirm all data checks have been completed before database lock.

The investigators and the institutions will permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other relevant documents (i.e. patients' case sheets, blood test reports, X-ray reports). Record keeping will be the responsibility of the investigators.

11. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. The chief investigator will review all presentations and publications arising from this study and decide authorship in accordance with accepted guidelines.

12. Insurance / Indemnity

The study will be indemnified by King's College London for negligent and non-negligent harm. In addition, the recruiting sites will have NHS indemnity.

13. Financial Aspects

The NIHR have supported the study through an EME programme grant award. The fistuloplasty balloons are supplied by C.R. Bard, Inc. who have no other role in the design, running or analysis of the trial.



PROTOCOL TITLE

Paclitaxel assisted balloon Angioplasty of Venous stenosis in haEmodialysis access (PAVE); A double-blind randomised controlled clinical trial to determine the efficacy of paclitaxel-assisted balloon angioplasty of venous stenoses in haemodialysis access

Trial Identifiers ISRCTN – 14284759 REC Number –
15/LO/0638

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- 1.2 Risks and benefits
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9. Ethics & Regulatory Approvals

10. Data Handling

11. Insurance / indemnity

12. Financial Aspects



Study Synopsis

Title	Paclitaxel assisted balloon Angioplasty of Venous stenosis in haEmodialysis access.
Protocol Short Title	PAVE Trial
Protocol Version number/ Date	Version 9.0 08/11/2018
Is the study a Pilot?	No
Study Hypothesis	The hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic arteriovenous fistulae.
Methodology	Double-blind multicentre randomised controlled trial
Sponsor name	King's College London / GSTT NHS Foundation Trust
Chief Investigator	Dr Michael Robson
REC number	15/LO/0638
Condition under investigation	Arteriovenous fistulae used for haemodialysis in patients with end stage kidney disease.
Purpose of clinical trial	RCT to assess the efficacy of additional paclitaxel-coated balloon fistuloplasty compared to plain balloon fistuloplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.
Number of Patients	211
Trial Design	Double-blind multicentre randomised controlled trial with variable follow up (minimum 1 year)
Endpoints	The primary endpoint is time to end of target lesion primary patency (TLPP). Secondary endpoints: 1. Angiographically determined late lumen loss 2. The rate of binary angiographic re-stenosis 3. Time to end of access circuit primary patency 4. Time to end of access circuit cumulative patency 5. Procedural success 6. Number of thrombosis events 7. Total number of interventions 8. Adverse events 9. Patient quality of life assessed by EQ-5D and POS-S Renal
Inclusion Criteria	1. Patients (18 years or over) who have a native AVF in the arm 2. An indication for a fistuloplasty as determined by the local clinical team 3. The access circuit is free of synthetic graft material or stents 4. A reduction of vessel diameter of $\geq 50\%$ measured angiographically, and a reference diameter of the outflow vein of at least 4 mm and less than the size of the largest available drug-coated balloon 5. A residual stenosis of $\leq 30\%$ after plain balloon fistuloplasty 6. A treatment segment, containing one or more lesions, which can be treated with ≤ 120 mm of a single drug-coated balloon
Exclusion Criteria	1. Patient unable to give informed consent 2. Patient unwilling or unable to comply with all study-related procedures 3. Systemic or local (to the fistula) infection treated for less than 10 days prior to the study procedure. 4. One or more lesions outside the treatment segment, with a reduction of vessel diameter of $\geq 50\%$ measured angiographically, in the same access circuit. The patient will also be excluded if any lesions outside the treatment segment are treated even if these are $<50\%$. 5. Location of stenosis central to the thoracic inlet 6. Thrombosed (failed) access circuit at time of treatment 7. Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children within two years of study treatment



	8. Known hypersensitivity or contraindication to contrast medium which cannot be adequately premedicated 9. Known hypersensitivity or contraindication to paclitaxel
Statistical Methodology and Analysis	To test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival we will use Cox-Proportional Hazards regression, on an intention to treat basis.

Device Name	Lutonix 035 Drug Coated Balloon PTA Catheter (Treatment) Ultraverse 035 PTA Dilatation Catheter (Placebo) Dorado PTA Dilatation Catheter (Plain balloon)
Manufacturer Name	C.R Bard, Inc.
Principle intended use	Angioplasty of stenosed blood vessels
Is the device CE-marked and used within its purpose?	Yes
Is the device currently used within the department?	Yes

Description and Maintenance and storage of device

The balloons will be stored under routine conditions in the radiology department.
 No special measures or maintenance is needed.

Are the devices registered on the DoH
 MIA Master Indemnity Scheme? Yes

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
Atm	Atmospheres (pressure)
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
ISRCTN	International Standard Randomised Controlled Trial Number
REC	Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
PTA	Percutaneous Transluminal Angioplasty
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
PCB	Paclitaxel-coated balloon
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

SSA	Site Specific Assessment
TLPP	Target Lesion primary patency
TMG	Trial Management Group
TSC	Trial Steering Committee

Disclaimer

This project is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and Social Care.

1. Introduction

1.1. Existing research

Vascular access for haemodialysis

The 2012 UK Renal Registry report (www.renalreg.com) found that 43.9% of patients with end-stage kidney disease in the UK are on haemodialysis. This equated to 365 patients per million population in the UK in 2011. This number has increased every year with an overall increase of 3.6% from 2006 to 2011. In order to perform haemodialysis, reliable vascular access is essential. It is universally agreed that the optimal form of access is a native arteriovenous fistula (AVF) are superior to synthetic arteriovenous grafts (AVGs) and tunnelled central venous catheters for haemodialysis access, AVFs and AVGs have limited lifespans. Data from the Dialysis Outcomes and Practice Study (DOPPS) showed that in the US the one year patency for AVFs and AVGs is 68% and 49% respectively. In Europe, one-year AVF survival was somewhat better at 83% but there is still a need for improvement [1].

Problems with vascular access are an important cause of morbidity and mortality in haemodialysis patients. In the US, it has been estimated that \$1bn per year is spent on vascular access and its complications [2]. A recent survey in the UK found that haemodialysis patients occupy 320,000 bed days per year, with 30% of admissions related to vascular access (Renal Association vascular access audit, available at www.renal.org). When thrombosis or stenosis occurs in an AVF or AVG, a central venous catheter may be used for several months until an AVF or AVG is formed and becomes usable. Data from the US has shown that the risk of invasive infection is increased 100 fold in haemodialysis patients compared to the general population. 85% of those diagnosed with an infection have an invasive device in situ. 90% of those diagnosed with an infection require hospitalisation and there is a 17% associated mortality [3]. It is therefore imperative to preserve each AVF or AVG for as long as possible and to minimise the use of central venous catheters.

The initial therapy for a stenosis in an AVF is radiological fistuloplasty. A major concern however is the longevity of this effect. Turmel-Rodrigues et al reported the outcomes of interventional salvage of dysfunctional and thrombosed haemodialysis circuits [4]. There were 220 cases in the dysfunctional AVF group. The 6, 12, 24 month primary patency (AVF working with no repeat intervention) reported were 67%, 51% and 37% for forearm AVF and 57%, 35% and 24% for upper arm AVF respectively. Bountouris et al. reported the outcomes after 159 percutaneous transluminal angioplasties (PTAs) in AVFs. The primary patency at 6, 12 and 24 months were 61%, 42% and 35% respectively [5]. Primary assisted patency (AVF working regardless of repeat intervention) was 89% and 85% at 6 and 12 months respectively. Although there have been some exceptions [6, 7], most other studies have reported similar primary patency rates of

around 40-50% at one year [8-10].

The biology of arteriovenous fistula dysfunction

In addition to the need for better interventions to reduce restenosis rates, there is also a need to better understand and identify the different types of response that occur following intervention. Neointimal hyperplasia leads to stenoses in the venous segments of AVFs, with the pathology characterised by an expansion of alpha smooth muscle actin positive myofibroblasts in the neointima [11]. In arteries, the contribution of bone-marrow derived cells to tissue repair depends on the nature and severity of injury [12]. The contribution of bone marrow cells to venous neointimal hyperplasia is not resolved and the data from animal studies are conflicting. Two studies using bone marrow transplantation with cells containing a green fluorescent protein (GFP) or β -galactosidase reporter gene, have suggested a minimal contribution of bone-marrow derived cells in mouse and rat model respectively [13, 14]. However a further study employing a murine vein graft, has suggested that at least 20% of neointimal cells may be bone marrow derived [15]. GFP positive cells were detected by a more sensitive PCR method and these technical differences were suggested as a reason for discrepancies with other studies.

In addition to these conflicting data on the origin of neointimal cells, it should be noted that none of the previous reports induced vein injury in a way that mirrors the changes induced by angioplasty. Instead, most have focussed on the development of primary stenosis in venous conduits undergoing arterialisation where endothelium is 'traumatised' or activated by changes in the flow characteristics of arterial blood to which it becomes exposed. Given the data from arterial studies, a contribution from bone marrow cells to the alpha smooth muscle actin producing cells in the hyperplastic neointima of a dysfunctional AV fistula is highly likely with the degree of trauma to the endothelium that would follow angioplasty. Angioplasty causes vessel wall damage with rupture of the junction between the intima and the media, with a burst of proliferation and repair. Much of our understanding of aggressive neointimal formation in this context comes from arterial studies [16], but similar pathology and an increase in proliferation has been shown in AVFs following venous angioplasty [17].

Paclitaxel exerts an antiproliferative effect by interfering with cell microtubule function [18]. Systemic administration of paclitaxel after angioplasty in the rat carotid artery showed that a significant reduction in neointimal proliferation could be achieved at doses much lower than antineoplastic levels [19]. In rat and human cultured cell models, paclitaxel inhibited vascular smooth muscle cell migration and proliferation [19, 20], consistent with its effects in vivo. As an alternative to systemic therapy, local drug delivery offers the advantages of allowing high local concentrations of drug at the treatment site while minimising systemic toxic effects. Proof of this possibility was initially shown using paclitaxel-coated stents in pig coronary arteries [21].

Recent advances in technology have allowed angioplasty balloons to be coated with paclitaxel. This allows local delivery of paclitaxel to the site of stenosis. A number of multi-centre randomised controlled trials in the coronary and peripheral arterial circulation have established the positive benefit of drug-coated balloons (DCBs) [22, 23]. A small pilot study has suggested efficacy in dialysis patients [24, 25]. In this study, 40 patients with dysfunctional AVFs or AVGs were randomised to receive either DCB or Plain Balloon Angioplasty (PBA). Primary unassisted patency (defined angiographically as a binary readout of <50% stenosis) in the DCB group was significantly better than the PBA group at 6 (70% v 25%) and 12 months (35% v 5%, $p < 0.001$) respectively. This study may be criticised on a number of points. These include the use of an angiographic rather than a clinical endpoint, the lack of blinding and independent angiographic core lab analysis and the very small sample size originally intended to test non-inferiority only

(with a wide 15% non-inferiority limit). In addition, a range of balloons was used in the control group for post-dilation after the paclitaxel-coated balloons, and these were not universally high pressure and non-compliant. This may have added variability to the outcome. Furthermore, the inclusion of both AVFs (35%) and AVGs (65%) may have resulted in significant confounding, given the difference in survival rates associated to the two types of access. Despite these limitations, the results suggested that a further study of efficacy was warranted, which is what we propose here.

The PAVE trial is the first large scale randomised controlled trial designed to test superiority of DCBs in native haemodialysis access circuits. Further, the impact on patient quality of life will be performed.

1.2. Risks and benefits

The risks for patients taking part in this study are minimal. The plain balloon fistuloplasty is standard of care and the additional intervention will be the use of a paclitaxel-coated balloon or control balloon following this initial dilatation. The paclitaxel-coated balloons that will be used are CE marked and there have been no safety concerns with their use. In the specific context of haemodialysis AVFs, the pilot study performed did not raise any safety concerns [24].

1.3. Rationale for current study:

The overriding aim of this study is preservation of vascular access for haemodialysis with a reduction in restenosis and the need for repeat fistuloplasties.

Clinical Trial

Our hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic AVFs. As detailed in section 1.1, this hypothesis is supported by what is known of the effects of paclitaxel on the biology of neointimal formation, results in trials involving coronary and peripheral arteries, and a pilot study vascular access for haemodialysis.

This need for repeat procedures following angioplasty is expensive and inconvenient for patients and is needed in around 60% of patients during the first year [5]. As detailed in our sample size calculation we predict that the use of paclitaxel coated balloons will lead to an avoidance of the need for repeat angioplasty. Repeat angioplasties will also have a negative effect on patient quality of life and a reduction in these will be a benefit in addition to the reduction in cost.

Collection of patient samples

Patient blood samples will also be collected within the setting of the clinical trial. This will form an important resource for future laboratory based studies on biomarkers and AVF outcomes.

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2. Trial Objectives, Design and Statistics

2.1. Trial objectives

The purpose of this RCT is to compare the efficacy of additional paclitaxel-coated balloon fistuloplasty versus plain balloon fistuloplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.

Primary Endpoint:

Time to end of target lesion primary patency

This is defined as patency with no re-intervention to the area 5mm proximal to, within, and 5 mm distal to, the index treatment segment. Target lesion primary patency ends when *any* of the following occur: (a) clinically driven re-intervention to the treatment segment; (b) thrombotic occlusion that includes the treatment segment; (c) surgical intervention that excludes the treatment segment from the access circuit; (d) abandonment of the AVF due to an inability to retreat the treatment segment.

In order to confirm there is a significant stenosis prior to fistuloplasty, Duplex ultrasound is encouraged but is not mandatory.

After the study treatment, occasionally there may be recoil or rupture necessitating further balloon angioplasty or stent placement. Providing further angioplasty and/or stent placement achieves a residual stenosis of less than 30%, these patients will remain in the study.

Referral for a repeat procedure will originate from the clinical team who are unaware of whether the patient received treatment with a paclitaxel-coated balloon or uncoated control balloon.

A different radiologist to the one performing the index procedure will perform repeat procedures when possible but it is not possible to guarantee this. Therefore the radiologist performing the

repeat procedure may have knowledge of whether the patient was treated with drug-coated balloon or placebo.

In order to ensure that there is no bias in the final decision to proceed with the repeat intervention in patients who have not yet reached the primary endpoint, pre-procedure fistulograms prior to potential re-intervention will undergo independent analysis. This will allow confirmation that a significant stenosis was found in all patients who received a repeat intervention.

Secondary Endpoints:

1. Angiographically determined late lumen loss.

This is the difference between the diameter of the treatment segment post-procedure and the diameter at 6 months as measured by an independent core laboratory. If a patient has a repeat procedure to the treatment segment before 6 months, then the pre-intervention images will be used for analysis and a fistulogram at 6 months will not be performed.

2. The rate of angiographic binary re-stenosis.

This is defined as the incidence of stenosis of at least 50% within the treated lesion at the 6 month follow-up fistulogram. If a patient has a repeat procedure to the index lesion before 6 months, then the pre-intervention images will be used for analysis and a fistulogram at 6 months will not be performed.

3. Time to end of access circuit primary patency

The access circuit is defined as starting at the arterial anastomosis and ending at the cavoatrial junction. Access circuit primary patency ends when *any* of the following occur: (a) access circuit thrombosis, (b) an intervention (either radiological or surgical) anywhere in the access circuit, or (c) the access circuit is abandoned due to an inability to treat any lesion.

4. Time to end of access circuit cumulative patency

Access circuit cumulative patency ends when the AVF is abandoned, regardless of radiological or surgical intervention, with or without a thrombosis event. Multiple/repetitive treatments for stenoses that restore patency are compatible with cumulative patency.

5. Procedural success (residual stenosis \leq 30% on completion fistulogram II, see section 4.4 below)

6. Number of thrombosis events

7. Total number of interventions

8. Adverse events (e.g. fistula rupture, infection)

9. Patient quality of life as assessed by the EuroQol EQ-5D generic health survey, and the disease specific Patient (or Palliative care) Outcome Scale symptom score-renal (POS-S Renal) [26].

2.2 Trial design

The study design used to achieve this will be a double-blind multicentre randomised controlled trial. We will recruit 211 patients over a three-year period. Patients will be followed up for a minimum of one year, and all patients will continue in the study until the last patient has



completed one year of follow up.



2.3 Trial schedule

	Pre-procedure	Procedure	Post-procedure ****															
			Day 1-3	mth 3	mth 6	mth 9	mth 12	mth 15	mth 18	mth 21	mth 24	mth 27	mth 30	mth 33	mth 36	mth 40	mth 44	mth 48
Patient registration and consent	x																	
Medical history (including indication for fistuloplasty)	x																	
Consideration of eligibility	x																	
Discussion and confirmation of potential eligibility with radiologist	x																	
Blood samples (taken on dialysis when possible)*****	x																	
Pre-procedure fistulogram *		x																
Plain balloon fistuloplasty			x															
Completion fistulogram I *				x														
Randomisation					X													
Study treatment							x											
Completion fistulogram II								x										
Protocol fistulogram																		
Follow up assessments ** ***					x	x	x	x	x	x	x	x	x	x	x	x	x	x
Quality of life assessments ***** (POS-S Renal and EQ-5D)	x					x		x										

* Prior to randomisation, eligibility will be reviewed based on the radiological findings on both the pre-procedure fistulogram and completion fistulogram I

**At each follow up assessment information to be checked or collected will include the following: target lesion primary patency, access circuit primary and cumulative patency, access circuit interventions, thrombosis events, patient medications, access circuit dysfunction, and adverse events

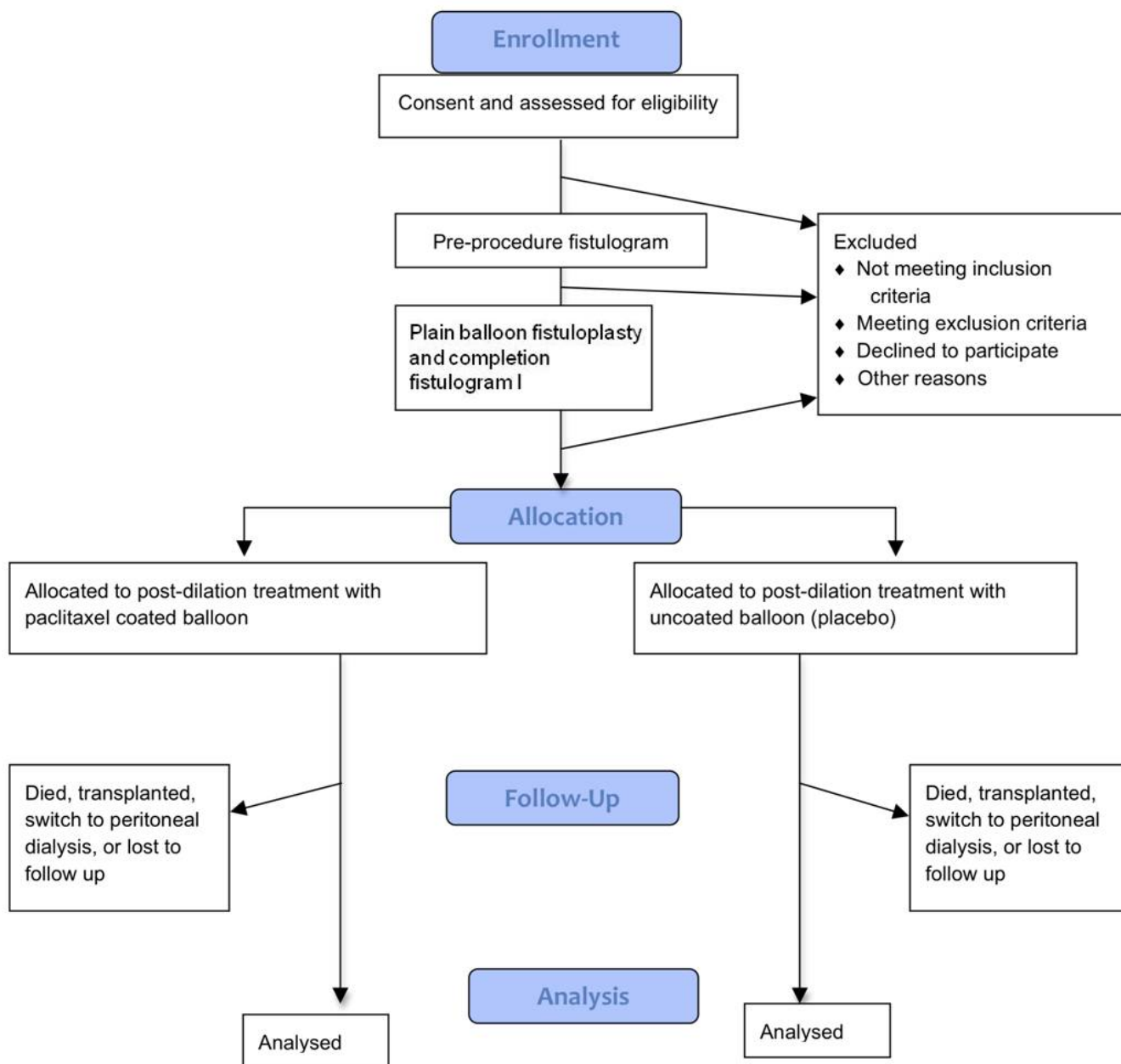
***Follow up will be for a minimum of 12 months and a maximum of 48 months

****Post-procedure study assessments occur every 3 months \pm 1 month; Day 1-3 blood sample to be taken at next dialysis session after procedure, if this falls on a weekend then blood to be taken at the next dialysis session after this

****Failure to complete the Quality of life assessments will not be deemed a protocol violation

*****Bloods may also be collected pre and 1-3 days post the protocol fistulogram at Guy's and St Thomas' only

2.4 Trial flowchart



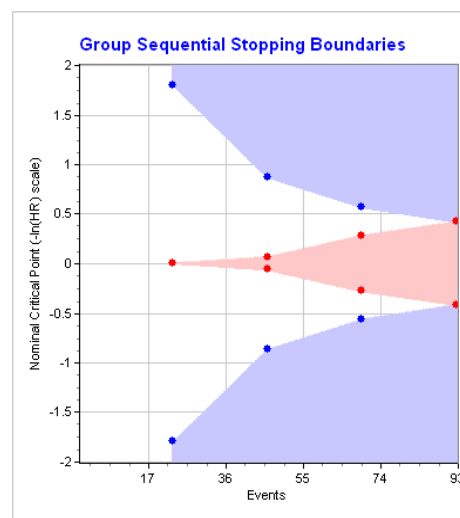
2.5 Trial statistics

Analysis of Primary Outcome: To test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival we will use Cox-Proportional Hazards regression, on an intention to treat basis. Primary analysis will be repeated using multivariate cox regression for the adjustment of the treatment effect size for the effect of known clinical covariates. Patients with TLPP at the end of follow up will be considered censored, as will those who receive a renal transplant, switch to peritoneal dialysis or are lost to follow up before the study end. Kaplan-Meier plots, hazard-ratio and its confidence interval will be used to describe the results.

Analysis of Secondary Outcomes: Effects on secondary outcomes will be analysed using the same strategy for time-to-event variables, and generalized linear models for binary and continuous outcome measures, adjusting for the effects of relevant covariates when appropriate. Continuous variables will be checked for normality, transformed if necessary or otherwise analysed using a Wilcoxon-signed-rank test for independent samples.

Missing Values and Drop-outs: If necessary, multiple imputation will be used for the imputation of missing values in baseline variables and secondary outcomes. Patients lost to follow up will be compared to patients who reach complete follow up in baseline characteristics and adverse events to test whether drop-outs are random.

Interim Analysis: Interim analysis of the primary outcome will be performed three times throughout the study, based on the cumulative number of failures of the treatment area, i.e. after 27, 54 and 81 events, expected approximately at 9, 14 and 19 months of study under the null, and at months 11, 17, and 23 under the alternative. Group sequential stopping boundaries have been calculated using a Lan-de-Mets spending function (with O'Brian-Fleming parameters), to allow early stopping for rejection of the null or the alternative hypotheses. Stopping in case of boundary crossing is non-binding.



3. Sample Size, Selection and Withdrawal of Subjects

3.1 Sample size

For the definition of the survival curve in the placebo balloon group, we assumed target lesion primary patency of 61%, 42%, and 35% at 6, 12 and 24 months respectively. This was consistent with published results [7] and with our own audit data. A hazard ratio (HR) of 0.5 was chosen as the minimum clinically relevant effect size. Katsanos et al. [21] found a HR of 0.3 for TLPP at 6 months; however, the confidence interval was broad and the effect size is expected to be closer to the null when AVGs are excluded. Based on these assumptions, it is expected that the paclitaxel coated balloon group will show 78%, 65%, and 59% survival of TLPP at 6, 12 and 24 months respectively. Recruiting 211 patients, with variable follow up, a minimum follow up of 1 year, and three interim analyses, will provide 94% power to detect a statistically significant difference between the two groups in TLPP survival with 2-sided 5% type I error rate. It is expected that 108 patients will experience fistula failure during the follow up period.



The required sample size has been estimated assuming cumulative 10% drop-out in each treatment arm by the end of the study, and recruitment of 2 patients per month (ppm) during the first three months, 8 ppm up to 7 months, and 12 ppm onwards. The expected accrual duration will be 36 months, and the maximum study duration (including follow-up) 50 months.

3.2 Inclusion criteria

1. Patients (18 years or over) who have a native AVF in the arm
2. An indication for a fistuloplasty as determined by the local clinical team
3. The access circuit is free of synthetic graft material or stents
4. A reduction of vessel diameter of $\geq 50\%$ measured angiographically, and a reference diameter of the outflow vein of at least 4 mm and less than the size of the largest available drug-coated balloon
5. A residual stenosis $\leq 30\%$ after plain balloon fistuloplasty
6. A treatment segment, containing one or more lesions, which can be treated with ≤ 120 mm of a single drug-coated balloon.

3.3 Exclusion criteria

1. Patient unable to give informed consent
2. Patient unwilling or unable to comply with all study-related procedures
3. Systemic or local (to the fistula) infection treated for less than 10 days prior to the study procedure
4. One or more lesions outside the treatment segment, with a reduction of vessel diameter of $\geq 50\%$ measured angiographically, in the same access circuit. The patient will also be excluded if any lesions outside the treatment segment are treated even if these are $<50\%$
5. Location of stenosis central to the thoracic inlet
6. Thrombosed (failed) access circuit at time of treatment
7. Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children, within two years of study treatment
8. Known hypersensitivity or contraindication to contrast medium which cannot be adequately premedicated
9. Known hypersensitivity or contraindication to paclitaxel



3.4 Criteria for withdrawal

Participants have the right to withdraw from the study at any time for any reason.

Participants will be withdrawn from the study if any of the following occur:

- Death of participant
- Participant receives a transplant
- Participant is changed from haemodialysis to peritoneal dialysis
- The fistula is ligated, abandoned, or thrombosed and not salvageable

The PI also has the right to withdraw patients from the study in the event of inter-current illness, AEs, SAE's, protocol violations, administrative reasons or other reasons, e.g. the participant is no longer being treated at a hospital included in the study.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Participants who wish to withdraw from 'treatment' will be asked to confirm whether they are still willing to provide study specific data and samples for scientific laboratory analysis according to the trial protocol.

4. Study Procedures

4.1 Screening procedures

Patients that may be eligible will be identified in a vascular access clinic and assessed by surgeons, specialist nurses and nephrologists.

In order to confirm there is a significant stenosis prior to angiography, a duplex ultrasound is encouraged but is not mandatory.

Consent will be taken after the patient has had sufficient time to read the information sheet, consider the trial and ask questions.

Eligibility criteria as listed above in section 3 will be assessed.

If the patient remains potentially eligible for the study, the radiologist who will perform the pre-procedure fistulogram will be informed.

4.2 The pre-procedure fistulogram

This will be take place immediately prior to the plain balloon fistuloplasty.

This will be performed in a dedicated Interventional Radiology suite equipped with digital subtraction angiogram, image overlay/roadmap post processing capabilities and ability to capture still and video



DICOM file data.

It will be performed through a sheath or cannula placed in the dialysis circuit according to the following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second (fps) if possible. If the equipment will not allow 3 fps then 2 fps is acceptable.
2. The entire access circuit from anastomosis to central vein covered in up to 3 stages
3. Medial epicondyle of humerus visible bony landmark on lower arm acquisition, acromioclavicular joint on upper arm and central acquisitions
4. Measurement ruler in view
5. Lower arm acquisition to include:
 - i. Anteroposterior Projection of anastomosis
 - ii. Oblique projection of anastomosis (specify oblique and craniocaudal angulation)
6. On the acquisition that best demonstrates the target lesion, the following measurements are made:
 - i. Peripheral (close to anastomosis) reference vessel diameter
 - ii. Minimum lumen diameter (MLD)
 - iii. Central reference vessel diameter

The radiologist will assess all inclusion and exclusion criteria, to decide if the patient remains eligible for the study.

4.3 The plain balloon fistuloplasty procedure

This is performed as standard of care. Prior to treatment 3000-5000 IU of heparin is administered. For all patients treatment has two components. The fistuloplasty procedure is performed with a dedicated plain balloon (*Bard Dorado*). Only if the anatomy of the lesion precludes the use of the *Bard Dorado*, then an alternative high pressure balloon may be used, providing it has a rated burst pressure of >18 Atm. The following criteria will be met:

1. Sized to nominal vein diameter
2. Up to 24 Atm to ensure obliteration of the lesion waist
3. Minimum duration of balloon inflation 1 minute.

Completion fistulogram I is performed after the plain balloon fistuloplasty to ensure adequate therapy according to the following specifications:

1. All fistulograms performed as digital subtraction acquisitions at 3 frames per second (fps) if possible. If the equipment will not allow 3 fps then 2 fps is acceptable.
2. Acquisition that demonstrates the target lesion matched as close as possible to the respective pre-procedure fistulogram acquisition
3. Measurement ruler in view



4. A core laboratory will make the following measurements at a later stage (these are not made by the radiologist performing the procedure)
 - i. Peripheral (close to anastomosis) reference vessel diameter
 - ii. Minimum lumen diameter (MLD)
 - iii. Central reference vessel diameter

The radiologist will assess all inclusion and exclusion criteria to decide if the patient remains eligible for the study.

4.4 Randomisation procedures

Randomisation will be at the level of the individual participants, minimising on radiologist performing the study procedure, whether the participant is currently on haemodialysis or not, and whether the participant has had a previous radiological intervention in the access circuit or not. This is performed with an 80% probability of allocating to the arm which reduces the imbalance. The allocation sequence will be generated dynamically. This way, the next allocation will only be generated and become known upon actioning a request from the study site staff.

Minimisation will be implemented using an independent web-based randomisation system hosted at the UKCRC registered clinical trials unit at KCL. Site staff will access the service via www.ctu.co.uk using a computer in the angiography room or an office nearby. It will be performed by the radiologist or their nominee, who will log into the system, enter the participant ID number, initials, date of birth, recruiting radiologist, whether the participant is currently on haemodialysis or not, and whether the participant has had a previous radiological intervention in the access circuit or not. Nominees must not be clinicians or nurses who may decide to refer the patient for re-intervention. Each randomiser will have unique user access, provided by the CTU upon the authorisation of the trial manager, once the delegation of authority form has been completed.

Once randomised, the system will automatically generate a confirmation email, which will be sent to relevant study staff in a blinded or unblinded format, depending on their role in the study.

If it is not possible to use the randomisation system, randomisation may occur using the toss of a coin in order to avoid losing the patient from the study. *This should only be needed, if at all, in specific and rare situations such as the CTU server being inaccessible.* This will be performed by two people with heads denoting drug-coated balloon, and tails denoting placebo. The CTU must be informed of the coin randomisation as soon as possible.

4.5 Study treatment

In the intervention arm, the second component is insertion of a single drug-coated balloon (Bard Lutonix).

If a single plain balloon was inflated at one location, the drug-coated balloon must be of identical diameter to the plain balloon and a minimum of 1 cm longer than the plain balloon (5 mm at either end).

In some cases more than one plain balloon may be used, or the same balloon may be inflated at different locations (eg to treat tandem lesions). In these cases, the drug-coated balloon must be of identical diameter to the largest diameter plain balloon used. The length of the drug-coated balloon must be a minimum of 1cm longer (5mm either end) than the entire segment of vein that has been in contact with plain balloon.



The drug-coated balloon will be inflated to nominal pressure at the lesion location for a minimum of 1 minute duration.

Instructions for use of the drug coated balloon are stringently adhered to ensure appropriate preparation and handling of the device.

In the control arm, an identical procedure is followed, but using a single placebo balloon that is not drug coated (*Bard Ultraverse*).

In both arms, image overlay/roadmap will be utilized to ensure that there is no geographical mismatch between the segments treated with the high and low-pressure balloons.

A completion fistulogram is performed (completion fistulogram II) to confirm no angiographically visible effect after treatment with the drug-coated or placebo balloon, according to the same specifications as fistulogram I in section 4.3. Procedural success is defined as a residual stenosis $\leq 30\%$ on completion fistulogram II.

The data file(s) containing the initial pre-procedure fistulogram, and completion fistulogram I and II will be sent to the lead study site with the patient's name replaced by the trial ID, and with each of the above groups of images clearly identified. Completion fistulogram II will then be sent to the independent angiographic laboratory for analysis.

4.6 Study assessments

These will occur every 3 months \pm 1 month. Follow up will be variable but for a minimum of 1 year and will continue for each patient while the study remains open. It is expected that the study will remain open for 4 years. These will involve a clinical assessment to take place either face-to-face or via a telephone conversation. Any face-to-face meetings will usually coincide with dialysis to avoid additional patient travel.

Data recorded for each study assessment will include the following: target lesion primary patency, access circuit primary and cumulative patency, access circuit interventions, patient medications, and adverse events.

At the 6-month study assessment, the trial team will check if referral for re-intervention is being considered based on clinical concerns.

The decision to perform a protocol fistulogram or not to, will be confirmed with the PI after discussion with relevant clinical colleagues, and a consideration of the points discussed in 4.7.1.

4.7 Radiology Assessments

4.7.1 The 6 month protocol fistulogram

Patients may be reimbursed for travel costs.

The protocol fistulogram will take place within 6 weeks of the 6 month study assessment if no clinical concerns are identified.

If clinical concerns are identified, then the protocol fistulogram may be delayed while the fistula is



assessed. If the outcome of this assessment is that an angiogram or re-intervention is not indicated, the patient may then have a protocol fistulogram scheduled. This must be no later than 9 months after the study intervention and treatment.

If the outcome of this assessment is that an angiogram or re-intervention is indicated, then a fistulogram \pm plasty will be performed according to usual clinical practice and the patient will not undergo a protocol fistulogram.

If a patient has required a repeat fistuloplasty to the treatment segment at or before 6 months then they will not undergo the 6 month protocol fistulogram.

If a patient declines the 6 month protocol fistulogram or does not have it for another reason, this will not be considered a protocol violation and the patient may continue in the study.

The 6 month protocol fistulogram *must* be performed by a radiologist other than the one who performed the index procedure to ensure that they are blind to which trial arm the participant belongs. With forward planning this should be possible but if it is not then the protocol fistulogram should not be performed.

The 6 month protocol fistulogram will be a diagnostic study only unless an unsuspected stenosis is found and the radiologist believes that it would be unethical not to intervene. This will not be considered a protocol violation and a fistula intervention form will need to be completed. The 6 month protocol fistulogram will follow the same specifications as the pre-procedure fistulogram in section 4.2.

The 6 month protocol fistulogram will be considered to be exclusively trial data. The result of the 6 month protocol fistulogram will not be made available (verbally or in writing) to the clinical team responsible for considering future referral of the patient for an intervention. The images will also not be available on the local radiology system. The images will be sent to the lead site in order to be forwarded to the independent core laboratory with the patient's name replaced by the trial ID.

4.7.2 Fistulograms performed for a clinical indication

In patients who have not yet reached the primary endpoint of the trial, pre-procedure fistulograms will follow the same specifications as the pre-procedure fistulogram specifications in section 4.2. The image file will be sent to the lead site with the patient details replaced by the trial PIN. This will be sent regardless of whether or not the fistulogram is followed by a fistuloplasty.

In patients who undergo an intervention, before 6 months, to the treatment segment, the pre-procedure fistulogram will be used (by the independent core laboratory) in place of the 6 month protocol fistulogram for analysis of the angiographic secondary endpoints.

4.8 End of Study Definition

The clinical trial will end when 211 patients have been recruited and all patients have completed at least one year of follow up.

The trial may be prematurely discontinued by the Sponsor, Funder, Chief Investigator or TSC on the basis of new safety information or for other reasons given by the DMC, TSC, REC. The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the TSC who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected.



5. Laboratories

5.1 Laboratory tests

There are no local laboratory tests that are required to provide data that directly relate to trial endpoints. A 10 ml blood sample will be requested at the three timepoints stated in the trial schedule (2.3), and is to be sent to the local clinical laboratory for a full blood count and to check the C-reactive protein level. If patients decline some or all of these samples, it will not be considered a protocol violation.

Blood (up to 90 ml) may be taken at each of the time points in the Trial Schedule in 2.3. These will be sent to the research laboratory of the CI where the blood will be separated. Research blood samples should not be taken from patients who are known to be hepatitis B sAg, hepatitis C IgG/ RNA, or HIV positive. DNA and RNA will be stored. Cells will be stored in aliquots in liquid nitrogen until thawed for analysis. Serum and/or plasma samples will be stored at -20°C or -80°C until thawed for analysis. Transport, separation and storage will be according to Standard Operating Procedures. It will not be considered a protocol violation if any of the blood samples are not taken, or are taken at different time points to those specified and patients may continue on the study.

If a patient is enrolled but not randomised, the patient will not continue in the clinical trial. However blood samples may continue to be taken for laboratory research (at the same time points as for patients remaining in the trial). Clinical data may also be recorded though this may not be on the eCRF system.

5.2 Independent Core Lab Analysis

The completion fistulogram II (taken after treatment with the DCB or placebo low pressure balloon) will be compared with the protocol 6 month fistulogram or with the pre-procedure fistulogram taken prior to a clinically driven re-intervention at the treatment segment if this is before 6 months. These will be analysed by an Independent Core Lab for the angiographic secondary endpoints.

In addition, in patients who have not yet reached the primary endpoint of the trial, clinically-driven pre-procedure fistulograms will be sent to the Independent Core Lab for analysis if they were performed by a radiologist who is not blind to the study treatment. This will be sent regardless of whether the fistulogram is followed by a fistuloplasty.

6. Assessment of Safety

We have been informed by the MHRA that the PAVE protocol does not fall within the Clinical Trial Regulations and therefore is not a drug trial. In addition, the drug-coated balloon is a CE-marked medical device, so prior regulatory approval from the MHRA is not needed.

Safety reporting will be in keeping with the requirements for research other than Clinical Trials of Investigational Medicinal Products.

A Serious Adverse Event (SAE) is an untoward occurrence that:

- a) results in death
- b) is life-threatening
- c) requires non-elective hospitalisation or prolongation of existing hospitalisation
- d) results in persistent or significant disability or incapacity
- e) consists of a congenital anomaly or birth defect



f) is otherwise considered medically significant by the investigator.

All SAEs will be reported by the local investigators on the SAE form to the Chief Investigator, immediately they become aware and within 24 hours at most. A planned or non-elective hospital admission does not need to be reported as an SAE unless the PI decides it should be.

Although it is not an SAE, any pregnancy or fathering of children that occurs within 2 years of the study treatment will be reported via the SAE system as below.

Reports of SAEs will be reviewed by the CI within 24 hours to assess whether the event is related to the research procedure and unexpected (a SUSAR) and if so, it will be onward reported to the REC and DMC within 15 days, in the format prescribed by NRES and published on the website.

Since the study treatment is local and not systemic, non-serious adverse events will be defined as events that the PI considers are directly related to the vascular access that has been treated. These should be recorded throughout the trial and will be captured in the eCRF at each study assessment.

7. Data Monitoring Committee

The membership will be decided by the CI and approved by the NIHR. The DMC includes a statistician and two other independent experts. They will receive a report of recruitment, serious and non-serious adverse events and a summary of accumulated clinical data from the trial statistician, and will meet in person or by telephone. They will report to the TSC who will usually meet in the two weeks following the DMC meeting. The DMC will meet at least annually during the study, approximately 2 weeks prior to the TSC. Additional meetings may take place at the time of interim analysis or in case of recruitment issues. The DMC is advisory to the TSC. The DMC charter will be drafted and agreed prior to recruitment. The Trial Statistician will prepare reports to the DMC.

8. Trial Steering Committee

The TSC will be convened in the post-award period. The membership will be decided by the CI and approved by the NIHR. The chair will be an independent expert. Members will include the CI, a patient representative, and two other independent experts. The TSC will meet at least annually during the study, approximately 2 weeks after the DMC. Additional meetings may take place at the time of interim analysis or in case of recruitment issues. The TSC is an executive committee. Terms of reference of the TSC will be agreed and documented prior to start of recruitment. The Trial Manager will prepare reports to the TSC.

9. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework.

This protocol and related documents will be submitted for review to the London-Chelsea Research Ethics Committee (REC).



The Chief Investigator will submit a final report at conclusion of the trial to the sponsor and the REC.

Annual progress reports will be submitted to the main REC for the study.

10. Data Handling

All samples will be anonymised before laboratory analysis. No patient-related data will be held in research laboratories.

During the study, any paper documents will be held in a locked filing cabinet in a locked office and retained for a minimum of 5 years following the end of the study.

Clinical and research data for the study will be stored on the eCRF system, hosted at the King's Clinical Trials Unit, KCL. The eCRF (InferMed MACRO) is GCP and FDA 21 CFR Part 11 compliant. Data entry staff at site will be provided with unique usernames and passwords to the system and will be trained in data entry by the trial manager. The trial manager will visit sites to review data on the system, raise discrepancies and confirm source data verification checks. All requests for access to the data entry system must be authorised by the trial manager. All requests for data exports must be authorised by the trial statistician. The trial manager will work with the CI and the trial statistician to ensure data is checked and cleaned on an ongoing basis and will confirm all data checks have been completed before database lock.

The investigators and the institutions will permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other relevant documents (i.e. patients' case sheets, blood test reports, X-ray reports). Record keeping will be the responsibility of the investigators.

11. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. The chief investigator will review all presentations and publications arising from this study and decide authorship in accordance with accepted guidelines.

12. Insurance / Indemnity

The study will be indemnified by King's College London for negligent and non-negligent harm. In addition, the recruiting sites will have NHS indemnity.

13. Financial Aspects

The NIHR have supported the study through an EME programme grant award. The fistuloplasty balloons are supplied by C.R. Bard, Inc. who have no other role in the design, running, or analysis of the trial.

VERSION CONTROL DOCUMENT – keep at front of Trial Master File

THE MOST UP-TO-DATE VERSION OF EACH DOCUMENT MUST BE PLACED UPPERMOST IN THE FILE – Retain all earlier versions for audit purposes and mark: ‘Superseded by Version (No) on (date)’ to avoid accidental use of wrong version.

Study Title (full):	Paclitaxel assisted balloon Angioplasty of Venous stenosis in haEmodialysis access		
Study Title (short):	PAVE		
Study Rec ref:	15/LO/0638	Chief Investigator:	Dr Michael Robson

PROTOCOL

VERSION No.	DATE	DATE APPROVED BY ETHICS	Changes
2.0	21 / 07 / 2015	18 / 08 / 2015	Version 2 it was approved and live before the first site opened to recruitment.
3.0	20 / 10 / 2015	03 / 11 / 2015	<p>Wording in the protocol describing trial procedures have been changed for clarification:</p> <ul style="list-style-type: none"> • “high pressure” changed to “plain” when describing the balloon used in the initial procedure • “treatment area” changed to “treatment segment” • The stratifier “whether or not the participant has had a previous intervention to the treatment segment” has been changed to “whether or not the participant has had a previous intervention in the access circuit” • The definition of the primary endpoint has been changed from “this is defined as patency with no reintervention to the area 5mm proximal within, and 5 mm distal to, the index treatment segment” to “this is defined as patency with no reintervention to the area 5mm proximal to, within, and 5 mm distal to the index treatment segment” <p>It has been clarified in inclusion criteria 1 that eligible participants should have an AVF that has been in use for 12 “consecutive” dialysis sessions (also listed in IRAS QA171)</p> <p>An additional secondary endpoint, “total number of interventions” has been added (also listed in IRAS QA11).</p> <p>The treatment procedure has been further clarified to ensure uniformity over all sites:</p> <ul style="list-style-type: none"> • The length of the treatment or placebo balloon relative to the plain balloon has been stated to ensure appropriate application of the treatment

			<ul style="list-style-type: none"> The dimensions of the treatment or placebo balloon should be determined by the largest plain balloon used in the procedure prior to the study treatment A further fistuloplasty immediately after study treatment to treat recoil does not constitute meeting the primary endpoint <p>The time in which the day 13 blood sample can be taken has been further defined in order to be more flexible, to account for out of office hours dialysis sessions</p> <p>The randomisation method has been specified as the minimisation method. We are using this method for three reasons:</p> <ul style="list-style-type: none"> Minimisation allows other radiologists at a site who don't perform the index procedure, and who will evaluate primary outcome, to be kept blinded. Using the alternative method, stratified block, where stratification would be i) by study site, and ii) whether or not the participant has had a previous intervention to the access circuit, the randomisation system would send all radiologists at a site the unblinded result. This is a limitation of the randomisation system we are using, but building a bespoke system would greatly delay the trial, thus using minimisation is appropriate. Minimisation ensures balance between groups, avoiding confounding due to radiologists effect. Minimisation is preferable to stratified block due to the large number of strata that result from the two stratifiers, and especially as the number of radiologists involved in the trial could change.
4.0	23 / 11 / 2015	N/A	<p>Non-substantial amendment to the protocol including the following changes:</p> <ul style="list-style-type: none"> a change in trial statistician re-wording in order to clarify procedures but no major change to warrant a substantial amendment.
5.0	08/03/2016	08/04/2016	<p>Protocol changes:</p> <p>Eligibility Criteria (study synopsis and section 3.2; IRAS QA17-1)</p> <ul style="list-style-type: none"> Inclusion criterion 1 has been changed to include all patients who have a native AVF in the arm, regardless of whether they are on haemodialysis or not. Previously we only included those patients who have been on haemodialysis for 12 consecutive sessions. These patients represent a prevalent population that would be relevant to the study. Most participants will start dialysis during the follow-up period and so the clinical endpoints of the trial will be unaffected. Even in those participants who do not start dialysis, their fistula can be assessed clinically and therefore clinical endpoints can still be assessed. Whether the participant is on haemodialysis or not at the time of randomisation will be an additional minimisation factor (section 4.4). The Participant Information Sheet, section 'Why have I been invited to take part?' has been

			<p>amended to reflect this change. The PIS version referenced on the consent form has been updated as a result.</p> <p>Plain Balloon Fistuloplasty Procedure (section 4.3):</p> <ul style="list-style-type: none"> We have specified that an alternative high pressure balloon to the one specified can be used only if the anatomy of the lesion is such that doesn't allow the specified balloon to be used initially. We have changed this so that participants with this type of lesion are not excluded in error. Subsequent changes in section 4.5 Study Treatment relate to this specification. For clarification, we have specified that a total of 3 plain balloon fistuloplasty treatments are allowed prior to the study treatment. <p>Fistulograms performed for a clinical indication (section 4.7.2)</p> <ul style="list-style-type: none"> We have clarified this section to ensure that all sites clearly understand which fistulograms images are required.
6.0	07/07/2016	31/08/2016	<p>1. Change in Project Manager (pg 2). Mrs Vikki Semik has resigned from her post and has been replaced by Dr Leanne Gardner as the Project Manager for PAVE.</p> <p>2. Change in inclusion and exclusion criteria to increase participant eligibility rates. An audit of eligibility rates for PAVE indicated that a considerable proportion of patients were ineligible for the trial due to synchronous lesions in their access circuit. As there are longer drug-coated balloons (greater than 60mm) available for use in the trial, we would like to include participants with one or more lesions than can be treated with up to 120mm of a single drug-coated balloon. This will improve eligibility rates and increase recruitment to the trial without the requirement for changes analysis of trial outcomes. Inclusion criteria 6 has been altered to include participants with a treatment segment containing one or more lesions that can be treated with greater than or equal to 120mm of a single drug-coated balloon (pg 4 and 15). Exclusion criteria 4 has been altered to exclude patients with one or more lesions outside the treatment segment (pg 4 and 15).</p> <p>3. Removal of details from the plain fistuloplasty procedure to increase participant eligibility rates. After consultation with a number of interventional radiologists, it was decided that if further balloon fistuloplasty treatment is required to obtain a positive result (residual stenosis is $\leq 30\%$), that the administration should not be restricted to two more times. Thus this paragraph was removed from the protocol (pg 17).</p> <p>4. Clarification of who will be performing the measurements required for the analysis of fistulograms performed in the trial. Details indicating that it will be a core laboratory that will make the fistulogram measurements have been added to the protocol (pg 18). This was added to the protocol because the interventional radiologists were unsure as to whether or not they were required to take these measurements.</p> <p>5. Details regarding the input of required information into the randomisation system have been added to the randomisation procedure section.</p> <p>In a previous amendment, we added that participants who were not currently on haemodialysis</p>

			<p>were eligible for the trial. Further detail was required in the protocol to indicate to the radiologists that this data must be entered into the randomisation system prior to randomising the participant (pg 18).</p> <p>6. Clarification of the length of time participants will be on the study: Additional information has been added to the protocol to indicate that participants will remain in the study until the last patient recruited has undergone one-year of follow up. The expected duration of the trial is 3 years but it will remain open until recruitment is complete and the last recruited patient has undergone one year of follow up.</p> <p>7. Clarification of procedures relating to the 6-month protocol fistulogram. We have altered the protocol to indicate that the decision to perform a protocol fistulogram, or not must be confirmed with the PI after discussion with relevant clinical colleagues (pg 19). We have also indicated that the 6-month protocol fistulogram must be performed within 6 weeks of the 6 month study assessment. This was increased from 2 to 6 weeks because additional time is required in some cases for the confirmation that a protocol fistulogram can be performed or not (pg 19). We have indicated that participants may be reimbursed for their travel expenses for attending the hospital for their 6-month protocol fistulogram. These participants will be attending the hospital specifically for this research-related procedure and not for clinical reasons. Thus we believe reimbursement for their travel expenses is justified in this case (pg 19).</p> <p>8. Clarification of procedures relating to fistulograms performed for a clinical reason. In section 2.1 (page 10) we have clarified that an independent assessment of the fistulogram will be performed though this may not necessarily be a core laboratory analysis in all cases. In section 4.7.2 (p20) we have clarified that all images from fistulograms performed for a clinical indication will be sent to the lead site. Some of these (prior to 6 months) may be used for to assess angiographic secondary endpoints as stated. Some may be sent to the independent core laboratory to demonstrate a lack of bias (as stated in section 5.2). Others may be used for quality control by the lead site.</p> <p>9. Collection of blood samples and clinical data from patients who have consented to the trial but are not randomised. We have added to the protocol that blood samples may continue to be taken and clinical data recorded, from consenting patients for laboratory research. These samples will be used for mechanistic studies that are planned on samples from patients who remain in the PAVE trial. Samples from patients excluded from the trial will remain useful for these studies which will examine factors in the blood pre and post fistuloplasty. The patient information sheet has also been amended to clarify this.</p> <p>10. Further clarification that the intervention procedure must be performed with only a single non-drug-coated or drug coated balloon. We have added the word "single" in two sentences of the Study Treatment section (pg. 18) to ensure that the radiologists are aware that they are only to use a single non-drug-coated or drug-coated balloon for the intervention.</p> <p>11. Changes to study documentation including PIS and consent form have also been made.</p>
7.0	26/01/2017	21/03/2017	Study Synopsis: Exclusion criterion Point 4. (page 4)

			<p>Additional detail has been added to criterion 4 to exclude patients if they have any additional lesions outside the treatment segment that are treated even if the reduction of vessel diameter of these lesions are <50%.</p> <p>3.3 Exclusion Criteria Point 4. (page 4)</p> <p>Additional detail has been added to criterion 4 to exclude patients if they have any additional lesions outside the treatment segment that are treated even if the reduction of vessel diameter of these lesions are <50%.</p> <p>3.4 Criteria for withdrawal (page 16)</p> <p>This section has been amended to update the criteria for withdrawal from the study. Participants will now be withdrawn from the study if their fistula is ligated, abandoned, or thrombosed and not salvageable. We no longer need to follow up these patients because the fistula that contained the treated lesion is no longer functioning and therefore does not need to be assessed.</p> <p>4.1 Screening procedures (page 16)</p> <p>In a previous amendment (Amendment 4 08/03/2016) we were given approval to consent participants in less than 24 hours prior to the procedure providing that the patients had sufficient time to considered taking part in the trial. This would allow us to take consent on the same day as the initial procedure, which is sometime necessary. These changes were approved by the REC. However this information was not updated in the protocol. These changes have now been made to the protocol indicating that consent will be taken after the patient has had sufficient time to read the information sheet, consider the trial and ask question.</p> <p>4.1 Screening procedures (page 16)</p> <p>All fistulograms are to be performed as digital subtraction acquisitions at 3 frames per second (fps). However at some units this is not possible. Thus we have indicated in the protocol that if equipment will not allow 3 fps then 2 fps is acceptable. The inclusion and exclusion criteria are examined at a number of different times during the screening period. Thus we have removed details when each of the criterion should be examined because most criterion are examined on a number of occasions.</p> <p>4.2 The pre-procedure fistulogram (page 17)</p> <p>Following the pre-procedure fistulogram the radiologist will assess all inclusion and exclusion criteria to decide if the patient remains eligible for the study. This has been clarified as some criterion needed need to be re-assessed following the procedure.</p> <p>4.2 The pre-procedure fistulogram (page 18)</p> <p>Following the plain balloon fistuloplasty procedure, the radiologist will again assess all inclusion and exclusion criteria to decide if the patient remains eligible for the study. This has been clarified as some criterion needed need to be re-assessed following this particular procedure.</p> <p>4.6 Study assessments (page 19)</p> <p>For clarification purposes regarding the 6 month study assessment, details about the requirements for the 6-month protocol fistulogram have been removed from this section and added to the following section 4.7.1.</p> <p>4.7.1 The 6 month protocol fistulogram (page 20)</p>
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			<p>This section has been rewritten for clarity. It indicates that the protocol fistulogram is performed if there are no clinical concerns identified and that it can be delayed while the fistula is assessed. Following assessment and if there are no concerns the 6-month protocol fistulogram can be performed no later than 9 months after the study intervention took place. If there are clinical concerns following assessment, then the 6 month protocol fistulogram will not take place and normal clinical practice will proceed. Patients may be reimbursed for travel costs if they have their 6 month protocol fistulogram (this was previously approved by the REC).</p> <p>5.1 Laboratory test (page 21)</p> <p>Previously, the REC had approved a reduction in the number of times a 10ml blood sample will be taken from four timepoints to three timepoints. This was updated in Table 2.3 but was not changed in the text of this section. This has now been updated. Blood samples are being taken before and after the study procedure and at the 3-month timepoint.</p>
8.0	13/12/2017	28/02/2018	<p>Section 2.1</p> <p>Primary Endpoint:</p> <p>Additional information has been added to the protocol for defining the primary endpoint. This information more clearly defines the assumptions required for time to end of target lesion primary patency.</p> <p>Section 4.5 Study Treatment:</p> <p>Additional information regarding the treatment procedure and use of plain balloons and treatment balloons has been added to the protocol. This was required to more clearly describe how the procedure is carried out correctly and to limit the number of protocol deviations due to inadequate description of the procedure. The additional text is highlighted in version 8 of the protocol attached.</p>
9.0	12/09/2018	21/12/2018	<p>Changes to the Protocol:</p> <p>Contact List: (Page 1):</p> <p>Updated details of the Sponsor and Co-Sponsor have been added to this section.</p> <p>The following changes have been made to the protocol to incorporate the additional 11 month study period, and to provide clarity of information:</p> <p>Section 2.2 (page 11)</p> <p>Previous Text: We will recruit 211 patients over a two-year period.</p> <p>New text: We will recruit 211 patients over a three-year period.</p> <p>Section 2.3 Trial Schedule (page 12)</p> <p>Following approval of the study extension, we have increased the number of follow up assessments in the Trial Schedule to month 48.</p> <p>We have also updated the Trial Schedule to confirm that failure to complete the Quality of life assessments will not be deemed a protocol violation.</p> <p>We have also added to the Trial Schedule that blood samples may also be collected pre and 1-3 days post the protocol fistulogram at Guy's and St. Thomas' only.</p> <p>Section 3.1 (page 14)</p> <p>Previous Text: The expected accrual duration will be 22 months, and the maximum study duration</p>

			<p>(including followup) 34 months.</p> <p>New text: The expected accrual duration will be 36 months, and the maximum study duration (including follow-up) 50 months.</p> <p>Section 4.6 (page 19)</p> <p>Previous Text: It is expected that the study will remain open for 3 years.</p> <p>New text: It is expected that the study will remain open for 4 years.</p> <p>Section 5.1 (page 21)</p> <p>For clarity, the second paragraph of this section has been updated to say Trial Schedule rather than table of events.</p> <p>Previous Text: Blood (up to 90 ml) may be taken at each of the time points in the table of events in 2.3.</p> <p>New text: Blood (up to 90 ml) may be taken at each of the time points in the Trial Schedule in 2.3.</p>
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PAVE Statistical Analysis Plan

Paclitaxel assisted balloon Angioplasty of Venous stenosis in haEmodialysis access (PAVE)

A double-blind randomised controlled clinical trial to determine the efficacy of paclitaxel-assisted balloon angioplasty of venous stenosis in haemodialysis access

Statistical Analysis Plan

Version 1.0

Version 1.0 started: 01/03/2016

ISRCTN: 14284759

This SAP has been written based on Protocol V4.0

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Signature..... Date

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1 QUANTITATIVE ANALYSIS PLAN

This document details the presentation and analysis strategy for the primary paper reporting results from the PAVE trial. Subsequent papers of a more exploratory nature will not be bound by this analysis plan but will be expected to follow the broad principles laid down for the principle paper(s). The principles are not intended to curtail exploratory analysis or to prohibit sensible statistical and reporting practices. Rather, they are intended to establish the primary scientific objective of the study, including the primary comparison and primary outcome and the strategy that will be followed as closely as possible, when analysing and reporting the trial.

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1.1 Description of the trial

This is a double-blind, multicentre RCT to assess the efficacy of additional paclitaxel-coated balloon angioplasty compared to high-pressure balloon angioplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.

1.1.1 Principal research objectives to be addressed

The hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic arteriovenous fistulae.

Primary objective

To assess time to end of target lesion primary patency (TLPP) following study treatment angioplasty.

Secondary objectives

To assess the difference between the two groups in:

1. Angiographically determined late lumen loss

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2. The rate of binary angiographic re-stenosis
3. Time to end of access circuit primary patency
4. Time to end of access circuit cumulative patency
5. Procedural success
6. Number of thrombosis events
7. Number of fistula interventions
8. Adverse events
9. Patient quality of life assessed by EQ-5D and POS-S Renal

A detailed description of trial objectives can be found in protocol section 2.1.

1.1.2 Trial design including blinding

The study is a double-blind multicentre randomised controlled trial, aiming to recruit 211 patients over a two-year period. Randomisation will be at the level of the individual participants, minimising on radiologist performing the study procedure and whether the participant has had a previous radiological intervention in the access circuit or not. Follow up will be variable and for a minimum of one year; and all patients will continue in the study until the last patient has completed one year of follow up.

1.1.3 Method of allocation of groups

Recruitment and pre-screening procedures are described in the protocol sections 4.1-4.3. Once the patient has completed the pre-procedure fistulogram, high-pressure balloon fistuloplasty, and the completion fistulogram I, the radiologist will assess if the residual stenosis is $\leq 30\%$; if this is the case then the patient will proceed to randomisation.

Randomisation will take place via a web based randomisation service, hosted at the UKCRC registered clinical trials unit at KCL. Site staff will access the service via www.ctu.co.uk using a computer in the angiography room or an office nearby. It will be performed by the radiologist performing the study procedure, or their nominee, and each randomiser will have unique user access. Access will be provided by the CTU upon the authorisation of the trial manager, once the delegation of authority form has been completed and relevant documentation regarding the individuals has been collected. Nominees must not be clinicians or nurses who may decide to refer the patient for re-intervention.

As explained in 1.1.2, patients will be randomized using minimisation; this is performed with an 80% probability of allocating to the arm which reduces the imbalance. The allocation sequence will be generated dynamically so that the next allocation will only be generated and become known upon actioning a request from the study site staff. Once randomised, the system will automatically generate an email confirmation, which will be sent to relevant study staff in a blinded or unblinded format, depending on their role in the study: an unblind email is received by the trial manager and the radiologist who is performing the randomisation; and a blind email is received by the principal investigator and research nurses.

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If it is not possible to use the randomisation system randomisation may occur using the toss of a coin in order to avoid losing the patient from the study. This should only be needed, if at all, in specific and rare situations such as the CTU server being inaccessible. This will be performed by two people with heads denoting drug-coated balloon, and tails denoting placebo. The CTU must be informed of the coin randomisation as soon as possible.

1.1.4 Duration of the treatment period

Study treatment is described in detail in the protocol section 4.5. This is a one-off treatment that is administered within one study visit. Any repeat intervention is considered an event and therefore the end of the follow up.

1.1.5 Frequency and duration of follow-up

Study assessments will take place every 3 months. Follow up will be variable but for a minimum of 1 year and a maximum of 3 years. These will involve a clinical assessment to take place either face-to-face or via a telephone conversation. Any face-to-face meetings will usually coincide with dialysis to avoid additional patient travel.

1.1.6 Visit windows

At the time of each 3-month study assessment, an allowance of one month will be given either side to measure follow-up. This one month visit window will be the same for recording data throughout the follow-up period, i.e. 3-36 months post randomisation.

1.1.7 Eligibility screening

Patients that may be eligible will be identified in a vascular access clinic and assessed by surgeons, specialist nurses and nephrologists. In order to confirm there is a significant stenosis prior to angiography, a duplex ultrasound is encouraged but is not mandatory. At least 24 hours after being given the patient information sheet and before entering the angiography room for the pre-procedure fistulogram, consent will be taken and eligibility criteria will be assessed.

Inclusion and exclusion criteria are described in sections 3.2 and 3.3 of the protocol.

The radiologist who will perform the pre-procedure fistulogram, high-pressure balloon fistuloplasty and completion fistulogram will be informed that the patient is potentially eligible for the study, and they will assess the remaining eligibility criteria.

1.1.8 Measures

Baseline

The following demographics will be measured at baseline:

- Age (years)
- Gender (male; female)
- Ethnicity (White; Black; Asian; Mixed; Other)

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The following clinical details will be measured at medical history screening:

- Current diabetes diagnosis (yes; no)
- Patient smoking history (current smoker; former smoker; never smoked)
- Coronary artery disease (yes; no)
- Peripheral vascular disease (yes; no)
- Time since end-stage kidney failure (months)
- Previous renal transplant(s) (number)
- Total accumulated time with a functional renal transplant (months)
- Total accumulated time patient has spent on haemodialysis (months)
- Total accumulated time patient has spent on peritoneal dialysis (months)
- Location of fistula (right arm; left arm)
- Type of native fistula (Radio-cephalic; Brachio-cephalic; Basilic vein transposition; Ulnar-cephalic)
- Time since fistula was formed (months)
- Time since fistula was first used (months)
- Current access circuit previously had a thrombosis (yes; no)
- Previous surgical interventions to the current access circuit (number)
- Previous fistuloplasties to the current access circuit (number)
- Primary indication for the index procedure (inadequate dialysis; poor fistula blood flow; prolonged bleeding; high venous pressures; low arterial pressure; difficulty needling; other evidence of fistula dysfunction)

The following clinical details will be measured at the pre-procedure fistulogram:

- Location of stenosis (juxta-anastomotic; venous segment; cephalic arch; after cephalic arch and not beyond the thoracic inlet; beyond the thoracic inlet)
- Degree of stenosis (5%)
- Length of stenosis (mm)
- Radiologist (initials)

The following clinical details will be measured at the treatment fistuloplasty:

- Index lesion vessel diameter (mm)
- Diameter of plain balloon used (mm)
- Length of plain balloon used (mm)
- Pressure to which used plain balloon was inflated (atm)
- Number of unsuccessful attempts at plain balloon fistuloplasty (0-2)
- Complications due to plain balloon fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Diameter of study treatment balloon used (mm)
- Length of study treatment balloon used (mm)
- Pressure to which study treatment balloon was inflated (atm)
- Complications of the study treatment fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Residual stenosis still 30% or less after study treatment (yes; no)
- Further fistuloplasty performed after study treatment (yes; no)

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- Type of balloon from further fistuloplasty (Dorado; other)
- Diameter of balloon from further fistuloplasty (mm)
- Length of balloon from further fistuloplasty (mm)
- Residual stenosis 30% or less after further fistuloplasty (yes; no)
- Complications due to further fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Radiologist (initials)

Primary outcome measures

The primary outcome measure is time to Target Lesion Primary Patency (TLPP). This will be measured in days post treatment fistuloplasty.

Secondary outcome measures

The secondary outcomes, as listed in 1.1.1, will be measured as follows:

1. Late lumen loss (mm); the difference between the diameter of the lesion at the completion fistulogram II (baseline) and at the protocol fistulogram (6 months)
2. Rate of binary angiographic re-stenosis (%); at the protocol fistulogram (6 months)
3. Time to loss of access circuit primary patency (days post treatment fistuloplasty)
4. Time to loss of access circuit cumulative patency (days post treatment fistuloplasty)
5. Procedural success (yes; no); stenosis $\leq 30\%$ at completion fistulogram II (baseline)
6. Thrombosis events (number); recorded as fistula interventions throughout the trial
7. Fistula interventions (number); recorded throughout the trial
8. Adverse events (number); recorded throughout the trial
9. Patient quality of life; EQ-5D and POS-S Renal scores

Adverse events

The following adverse event measures will be collected at 6 and 12 months post randomisation, and at withdrawal, where applicable:

- Adverse Event (Oedema of hand or arm; Pseudoaneurysm; Haematoma; Distal Ischaemia; Neurological complications; Infection localised to fistula; Central venous catheter insertions; other)
- Duration of event (days)
- Intensity (mild; moderate; severe)
- Outcome (resolved; resolved with sequelae; ongoing; death; unknown)
- Related to study intervention (definite; probable; possible; remote; none)
- Serious Adverse Event (yes; no)
- Ongoing at end of study (yes; no)

Please refer to section 2 for the schedule of assessments and measures.

1.1.9 Sample size estimation (including clinical significance)

For the definition of the survival curve in the placebo balloon group, we assumed target lesion primary patency of 61%, 42%, and 35% at 6, 12 and 24 months respectively. This was consistent with published results {Bountouris:2014dy, Tessitore:2003ty} and with our own audit data. A hazard ratio (HR) of 0.5 was chosen as the minimum clinically relevant effect

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size {Katsanos:2012hd} found a HR of 0.3 for Target Lesion Primary Patency at 6 months; however, the confidence interval was broad and the effect size is expected to be closer to the null when AVGs are excluded. Based on these assumptions, it is expected that the paclitaxel coated balloon group will show 78%, 65%, and 59% survival of TLPP at 6, 12 and 24 months respectively. Recruiting 211 patients, with variable follow up, a minimum follow up of 1 year, and three interim analyses, will provide 94% power to detect a statistically significant difference between the two groups in TLPP survival with 2-sided 5% type I error rate. It is expected that 108 patients will experience fistula failure during the follow up period, 66 in the control arm, and 42 in the intervention arm.

The required sample size has been estimated assuming cumulative 10% drop-out in each treatment arm by the end of the study, which would result in 6 patients in the treatment arm, and 3 in the control arm. We have planned for a recruitment rate of 2 patients per month (ppm) during the first three months, 8 ppm up to 7 months, and 12 ppm onwards. The expected accrual duration will be 22 months, and the maximum study duration (including follow-up) 34 months.

1.1.10 Brief description of proposed analyses

Analyses will be carried out by the trial statistician (ER) once the database has been locked. Data will be analysed with an intention-to-treat approach (i.e. analyse all those with data in groups as randomised irrespective of treatment received).

There will be descriptive statistics reported on the measures mentioned in 1.1.8, with an aim to comparing the treatment arms, and to review the patient demographics.

For the primary analysis, to test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival, Cox-Proportional Hazards regression will be used. This will be repeated using multivariate cox regression for the adjustment of the treatment effect size for the effect of known clinical covariates; which are listed in detail in section 1.3.2.

Effects on secondary outcomes will be analysed using the same strategy for time-to-event variables, and generalized linear models for binary and continuous outcome measures, adjusting for the effects of relevant covariates when appropriate.

Interim analysis of the primary outcome will be performed three times throughout the study, based on the cumulative number of failures of the treatment area.

Further details of the analyses are given later on in this document.

Data summaries and analyses will be carried out in Stata 14.0.

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1.2 Data analysis plan – Data description

1.2.1 Recruitment, eligibility and representativeness of patients

A CONSORT flow chart will be constructed – see Figure 1. The number of patients will be summarised using the following categories: total number of patients screened; eligible; consenting; and randomised.

Then by treatment arm: patients compliant and non-compliant with intervention; continuing through the trial; withdrawing; lost to follow-up; and excluded or analysed.

Compliance (adherence) is defined as receiving the following procedures: plain balloon fistuloplasty; completion fistulogram I; study treatment fistuloplasty; and completion fistulogram II.

A summary of the number of patients compliant with the study treatment will be provided and stratified by study centre.

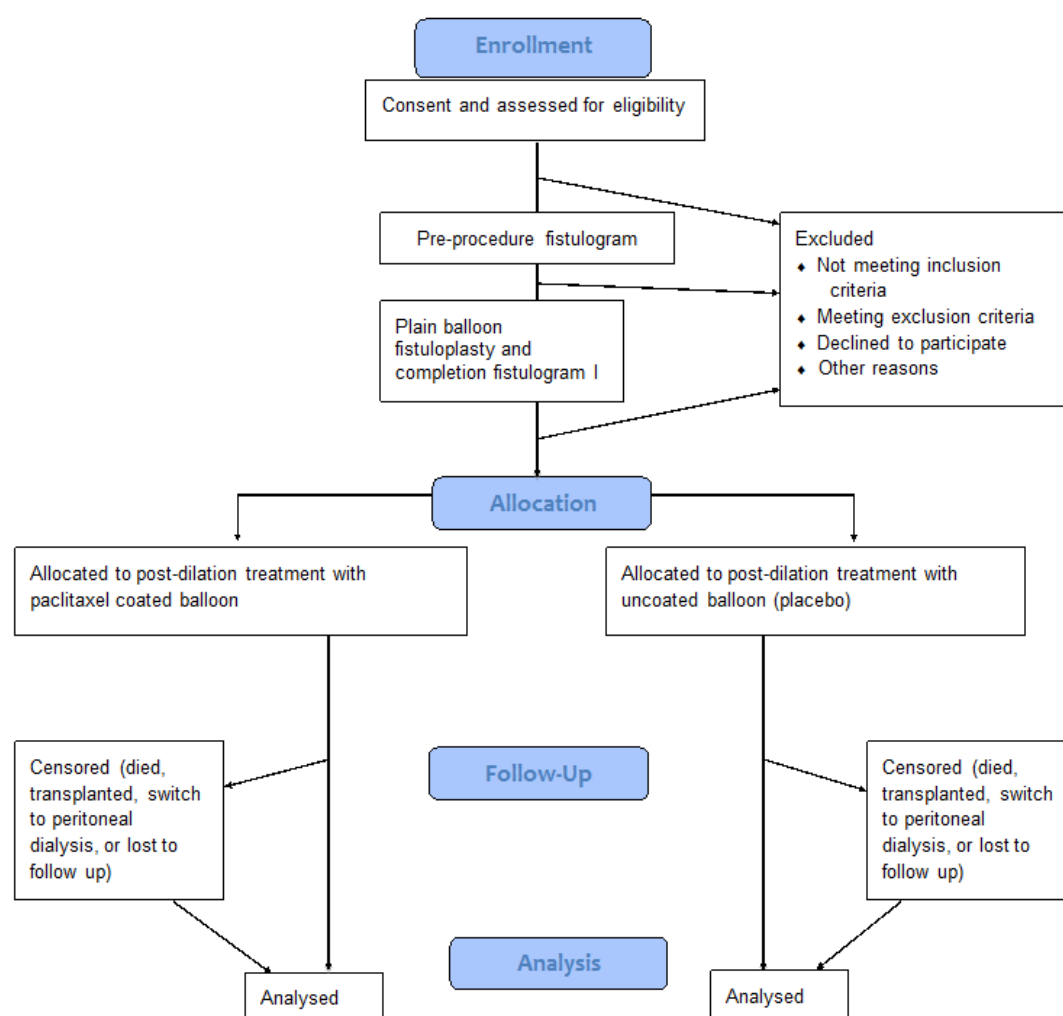


Figure 1. Template CONSORT diagram for PAVE trial

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1.2.2 Baseline comparability of randomised groups

All baseline variables listed under measures in section 1.1.8 will be reported by trial arm and overall. They will be grouped into patient demographics and patient clinical information, and reported as: minimums and maximums, means and standard deviation, medians and quartiles for continuous variables as appropriate; and frequencies and proportions for categorical variables. No significance testing will be used to test baseline differences between the trial arms.

1.2.3 Adherence to allocated treatment and treatment fidelity

Adherence to allocated treatment (compliant versus non-compliant), as described in 1.2.1, and the reasons for not completing the treatment process will be summarised using the treatment fistuloplasty form. Adherence will be compared between trial arm using baseline variables; and the reasons for withdrawal from treatment will be summarised.

1.2.4 Loss to follow-up and other missing data

Withdrawal from trial follow-up (attrition rate) will be reported by intervention group, including reasons for withdrawal. The proportions of participants missing each variable will be summarised in each arm and at each study visit.

If necessary, multiple imputation will be used for the imputation of missing values in baseline variables and secondary outcomes. Patients with TLPP at the end of follow up will be considered censored, as will those who receive a renal transplant, switch to peritoneal dialysis or are lost to follow up before the study end.

The baseline characteristics and adverse events of patients lost to follow up will be compared to those with complete follow up data. The relationship between these and missing data will be investigated graphically to see if baseline characteristics or adverse events predict missing, i.e. drop-outs are not random.

1.2.5 Adverse event reporting

Adverse events (AE), adverse reactions (AR), serious adverse events (SAE) and serious adverse reactions (SAR) will be summarised by trial arm and overall.

1.2.6 Assessment of outcome measures (unblinding)

Outcome assessors and the trial statistician are being kept blind to treatment allocation.

1.2.7 Descriptive statistics for outcome measures

The primary and secondary outcomes as listed in section 1.1.8 will be described by treatment group and time point. Means and standard deviations or medians and interquartile ranges will be used for continuous variables, where relevant; this will check whether continuous outcomes can be assumed normally distributed. Kaplan-Meier plots,

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hazard-ratio and its confidence interval will be used to describe the time to event results. Frequencies and proportions will be used to describe binary variables.

1.3 Data analysis plan – Inferential analysis

1.3.1 Aims of formal inferences

The formal statistical analyses will estimate the differences in relevant variables (time to event, quality of life) between patients randomised to the paclitaxel-coated balloon angioplasty compared to high-pressure placebo balloon angioplasty, by intention to treat.

As mentioned in section 1.2.4, for the primary outcome and other time to event variables, patients lost to follow-up will be right censored; this means they are counted as not having experienced end of target lesion primary patency, or the relevant event, for the period of time we have data on them. If dropout is related to both outcome and treatment, then dropouts may bias the results.

Group difference estimates and associated 95% confidence intervals will be reported. The trial statistician will remain blind until the main analyses have been completed. The overall significance level will be 5% (two-sided) for the primary and secondary outcomes.

Significance level of final analysis of primary outcome will be determined by the alpha spending function used to plan interim analyses.

Details on the methods for handling missing data are given in sections 1.3.8.

Sensitivity analyses will be used to assess the robustness of conclusions; please refer to section 1.4 for details of the planned sensitivity and subgroup analyses.

1.3.2 Analysis of the primary outcome

The analysis population will include all patients randomised with sufficient information to carry out the analysis, i.e. complete primary outcome data and minimisation factors. The primary outcome is time to end of target lesion primary patency (TLPP); measured as days post randomisation. For the purpose of the primary outcome analysis, this will be taken as recorded by the target lesion primary patency form.

Expected time to end of TLPP will be calculated using the hazard ratio estimated by the model explained below. Survival analysis methods will be used to compare the primary outcome for the two groups as this can factor in censoring and time.

Kaplan-Meier plots will be used to graphically illustrate and compare the observed probabilities of target lesion primary patency past certain times in the trial period, taking into account censoring, for the two trial arms. This is a non-parametric estimate of the survival function over the analysis time, and will also be used to check the Cox proportionality assumption – see section 1.3.10.

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Cox-Proportional Hazards regression will be used to model the effect of predictors and covariates on the hazard rate and estimate the relative risk by trial arm. This will be compared to an initial estimate from the null model where the model will be fitted without any covariates. Model components included in the primary model will be a baseline hazard function that is unspecified but positive; previous radiological intervention in the access circuit; trial centre; trial arm; observed study time (length of time between patient entering and exiting study); and a trial arm*observed time interaction term. The interaction term allows for variable follow-up time effects.

A secondary adjusted analysis will be fit to evaluate the impact of baseline covariates on the size of the treatment effect. The covariates considered will be: baseline characteristics (ethnicity; age; diabetes diagnosis; and smoking history) and clinical variables at baseline (total time on haemodialysis; time since end stage kidney failure; type of native fistula; previous circuit intervention; and location of stenosis).

The relationship between baseline variables and missing outcome data will be assessed using logistic regression with an outcome variable that represents whether outcome data are present or missing. Should any baseline variables be predictive of missing then these will be included in the primary analysis Cox regression models as further covariates.

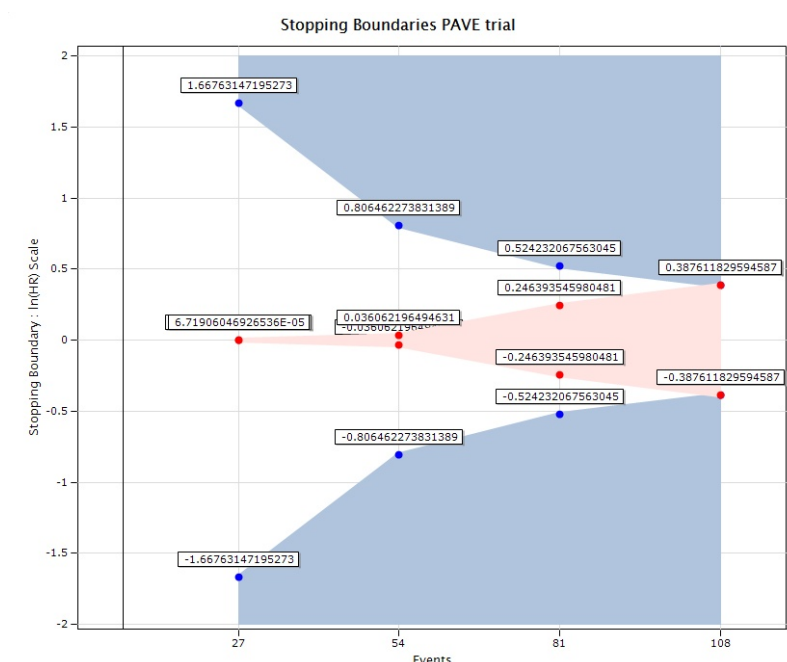
1.3.3 Interim analysis

Interim analysis of the primary outcome will be performed three times throughout the study, based on the cumulative number of failures in the primary outcome, i.e. after 27, 54 and 81 events, expected approximately at 9, 14 and 19 months of study under the null, and at months 11, 17, and 23 under the alternative hypothesis. Group sequential stopping boundaries have been calculated using a Lan-de-Mets spending function (with O'Brien-Fleming parameters), to allow early stopping for rejection of the null or the alternative hypotheses. Stopping in case of boundary crossing is non-binding and will be discussed with the DMEC members during a closed session that does not include any trial members who are blinded.

The Hazard Ratio used to evaluate the crossing of stopping boundaries will be calculated with a Cox-proportional hazards regression that includes centre, and presence or absence of previous interventions as covariates, as well as treatment group as independent variable of interest.

Stopping boundaries are displayed in the figure below:

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The table below shows further details of the stopping boundaries, including expected probability of crossing at each interim, and cumulative Alpha and Beta spent.

Look #	Info. Fraction	Events	Cum. α Spent	Cum. β Spent	Boundaries			
					Efficacy Boundary		Futility Boundary	
					Upper	Lower	Upper	Lower
1	0.25	27	0	0	5.3	0.189	1	1
2	0.5	54	0.003	0.004	2.24	0.446	1.037	0.965
3	0.75	81	0.019	0.024	1.689	0.592	1.279	0.782
4	1	108	0.05	0.059	1.473	0.679	1.473	0.679

Look #	Sample Size		Analysis Time		Incremental Boundary Crossing Probabilities					
					Under H0: $\ln(\lambda_t/\lambda_c) = 1$			Under H1: $\ln(\lambda_t/\lambda_c) = 0.49...$		
	Under H0	Under H1	Under H0	Under H1	Efficacy		Futility	Efficacy		Futility
					Upper	Lower		Upper	Lower	
1	91	106	9.483	10.968	0	0	0	0	0.006	0
2	140	163	14.522	16.985	0.002	0.002	0.105	0	0.333	0.004
3	185	211	19.213	22.651	0.008	0.008	0.633	0	0.44	0.02
4	211	211	23.95	33.792	0.014	0.014	0.214	0	0.162	0.035

Stopping boundaries in the table are expressed in the HR scale.

Test statistics for interim analysis will be calculated with standard statistics software packages (R or Stata), and entered into the interim monitoring tool of the East software in order to check crossing of boundaries, and calculate effect size and conditional power.

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Interim analyses will be programmed by the trial statistician, but run and summarised by an independent statistician.

1.3.4 Analysis of secondary outcomes

Secondary patient outcomes relating to time-to-event variables, for example, time to end of access circuit primary patency, will be analysed using Cox regression models in a similar method to above.

Continuous variables such as POS-S Renal score for quality of life, will be checked for normality, transformed if necessary and analysed using linear regression models. Otherwise, they will be analysed using a Wilcoxon-signed-rank test for independent samples. Logistic regression models will be used for binary secondary outcomes, for example, procedural success (rate of binary angiographic re-stenosis $\geq 50\%$) at the six month protocol fistulogram.

Similarly to the primary outcome analysis, covariates considered in the models will include: baseline measure of outcome variable, where applicable; minimisation factors; trial arm; and time in study. An interaction term will also be included between observed study time and study treatment, as above.

1.3.5 Stratification and clustering

Randomisation is on the patient level, minimising on radiologist performing the study treatment and previous radiological intervention to treatment area or not; therefore these variables will be included as covariates in the modelling process, as mentioned in section 1.3.2. However, the data should not have a clustered structure so this does not need to be accounted for.

1.3.6 Missing items in scales and subscales

The number (%) with complete data will be reported. The ideal approach would be to use missing value guidance provided for scales.

1.3.7 Missing baseline data

We do not anticipate missing values in pre-randomisation variables. However, if we encounter missing baseline values then these can be singly imputed according to White and Thompson^[3] without incurring bias of the treatment effect estimate.

1.3.8 Censoring and missing outcome data

For time to event outcomes, patient data is considered censored when the patient is withdrawn from follow-up, i.e. it is only known that the amount of time to event for that patient is greater than some value. Censoring will also happen at the end of the study, if the patient does not experience the primary endpoint before end of follow-up. In the analysis, the censored observations will be included in the number of patients at risk in respect to their observed study time (survival time).

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For non-time to event outcomes, missing post-randomisation assessments will be dealt with by fitting generalised mixed models to all the available data using maximum likelihood methods. Such an approach provides valid inferences under the assumption that the missing data mechanism is ignorable (or MAR). This allows for missingness at later times to be predicted by outcome values at earlier times. If post treatment variables such as compliance with study procedures are found to be predictive of drop out, multiple imputation will be considered.

1.3.9 Method for handling multiple comparisons

Analysis of secondary outcomes is considered exploratory, and therefore there will be no correction for multiple testing. However, care should be given to the interpretation of inference for the numerous secondary outcomes and it may be necessary to assess the agreement between similar outcome measures. Cohen's Kappa statistic and/or Spearman's rank correlation coefficients may be used to test for inter-participant reliability and to measure the degree of linear association between two outcomes. For example, angiographically determined late lumen loss and the rate of binary angiographic re-stenosis would be expected to be highly predictive of one another.

1.3.10 Method for handling non-compliance

In addition to the primary intention-to-treat analysis the effect of actually receiving treatment as defined in the protocol will also be estimated.

There is not expected to be a problem with non-compliance due to the design of the trial.

1.3.11 Model assumption checks

In order to assess the adequacy of the Cox regression models for the primary outcome and time-to-event secondary outcomes, the main assumption to test for is proportionality; the Kaplan-Meier plots will be used to check if the curves for the two trial arms are the same shape, and if the separation of the curves remains proportionate throughout the analysis period.

In addition, time-dependent covariates will be generated by creating interactions of the predictors and function of survival time; if these are significant then the predictors are not proportional.

If the assumption for proportionality is violated then the consequence this has on the results can be checked. The Cox model can be stratified according to the variables with non-proportional hazards to see whether that changes the hazard ratios for the variables of interest; if it still does, then it may be necessary to use an alternative model. One parametric alternative is the Royston-Parmar model, which is more flexible and can fit a non-proportional hazards model.

For the other secondary outcomes regression residuals will be plotted to check for normality and outliers, where applicable.

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1.4 Sensitivity analyses

1.4.1 Planned sensitivity analyses

A sensitivity analysis will be performed using adjudicated data from the core lab readings, in comparison to the primary analysis where the events reported in the trial will be used. This will assess the robustness of the trial findings by clarifying whether the primary analysis conclusions are impacted by any methodological issues, such as outcome definitions.

1.4.2 Planned subgroup analyses

Subgroup analyses will be carried out to assess whether the observed effect is consistent across patient categories; to do this, an interaction term will be included in the Cox proportional hazards model between the exposure (study treatment group) and the subgroup variable.

The planned subgroups will be: second minimisation factor (previous radiological intervention to the treatment area or not); smoking history (current smoker, former smoker, never smoked); baseline diabetes diagnosis (yes, no); current total time on haemodialysis (quartiles); total time since end stage kidney failure (quartiles); type of native fistula (Radio-cephalic, Brachio-cephalic, Basilic vein transposition, Ulnar-cephalic); and location of stenosis (juxta-anastomotic, venous segment, cephalic arch, between cephalic arch and thoracic inlet).

1.4.3 Competing risks analyses

To assess the influence of events that may prevent other events from being observed, competing risks analyses will be planned to adjust for these. Specifically, 'irrelevant' deaths and re-transplantations will be defined as competing risks rather than censored events. The cause of death will be checked from hospital notes and/or death certificates.

1.4.4 Exploratory analyses

This analysis plan does not cover secondary exploratory analysis. Exploratory mediator and moderator analyses may be performed after the primary trial data analysis.


1.5 Software

Data management: An online data collection system for clinical trials (MACRO; InferMed Ltd) will be used. This is hosted on a dedicated server at KCL and managed by the KCTU. The KCTU Data Manager will extract data periodically as needed and requests will usually be made by the trial statistician. There will be several database extracts throughout the trial for each DMEC Report, and a final extract after data lock. Data will be provided in comma separated (.csv) format.

Statistical analysis: Stata and or R will be used for data description and inferential analysis.

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2 SCHEDULE OF ASSESSMENTS AND MEASURES

	Variable count	Enrolment	Treatment day (Day 0)	Day 1-3	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	Month 27	Month 30	Month 33	Month 36	Ongoing
01. Registration form	5	X															
02. Eligibility form	14	X															
03. Medical History form	19	X															
04. Haematology and Biochemistry form	11	X		X	X	X											
05. Pre-procedure Fistulogram form	8		X														
06. Randomisation form	4		X														
07. Treatment Fistuloplasty form	46		X														
08. Fistula Intervention form (repeating)	32																X
09. Month 6 Fistula Function form	9					X											
10. Protocol Fistulogram form	11					X											
11. POS-S Renal questionnaire	25	X				X		X									
12. EQ-5D questionnaire	6	X				X		X									
13. Medications form	17	X			X	X	X	X	X	X	X	X	X	X	X	X	
14. Adverse Events form	9																X
15. Withdrawal form	5																X
16. Status form	5				X	X	X	X	X	X	X	X	X	X	X	X	
17. Loss of Patency form (repeating)	9																X

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3 REFERENCE LIST

1. Bountouris:2014dy, Tessitore:2003ty	8
2. Katsanos:2012hd	8
3. White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials 2005;24(7): 993–1007.....	15

PAVE Statistical Analysis Plan

Paclitaxel assisted balloon Angioplasty of Venous stenosis in haEmodialysis access (PAVE)

A double-blind randomised controlled clinical trial to determine the efficacy of paclitaxel-assisted balloon angioplasty of venous stenosis in haemodialysis access

Statistical Analysis Plan

Version 2.0

Version 2.0 started: 26/09/2018

ISRCTN: 14284759

This SAP has been written based on Protocol V8.0

Trial Statistician: Emily Robinson

Signature 


Date 15/11/2018

Chief Investigator: Dr Michael Robson

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Date 14/05/2019

Trial Steering Committee Chair: Dr Richard Haynes

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Date 15/11/2018

Data Monitoring Committee Statistician: Dr Isabel Reading

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1 QUANTITATIVE ANALYSIS PLAN

This document details the presentation and analysis strategy for the primary paper reporting results from the PAVE trial. Subsequent papers of a more exploratory nature will not be bound by this analysis plan but will be expected to follow the broad principles laid down for the principle paper(s). The principles are not intended to curtail exploratory analysis or to prohibit sensible statistical and reporting practices. Rather, they are intended to establish the primary scientific objective of the study, including the primary comparison and primary outcome and the strategy that will be followed as closely as possible, when analysing and reporting the trial.

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1.1 Description of the trial

This is a double-blind, multicentre RCT to assess the efficacy of additional paclitaxel-coated balloon angioplasty compared to high-pressure balloon angioplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis.

1.1.1 Principal research objectives to be addressed

The hypothesis is that we will demonstrate efficacy of paclitaxel-coated balloons in improving outcomes after fistuloplasty of stenotic arteriovenous fistulae.

Primary objective

To assess time to end of target lesion primary patency (TLPP) following study treatment angioplasty.

Secondary objectives

To assess the difference between the two groups in:

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1. Angiographically determined late lumen loss
2. The rate of binary angiographic re-stenosis
3. Time to end of access circuit primary patency
4. Time to end of access circuit cumulative patency
5. Procedural success
6. Number of thrombosis events
7. Number of fistula interventions
8. Adverse events
9. Patient quality of life assessed by EQ-5D and POS-S Renal

A detailed description of trial objectives can be found in protocol section 2.1.

1.1.2 Trial design including blinding

The study is a double-blind multicentre randomised controlled trial, aiming to recruit 211 patients over a two-year period. Randomisation will be at the level of the individual participants, minimising on radiologist performing the study procedure; whether the patient has had a previous radiological intervention in the access circuit or not; and whether the patient is currently on haemodialysis. Follow up will be variable and for a minimum of one year; and all patients will continue in the study until the last patient has completed one year of follow up.

1.1.3 Method of allocation of groups

Recruitment and pre-screening procedures are described in the protocol sections 4.1-4.3. Once the patient has completed the pre-procedure fistulogram, high-pressure balloon fistuloplasty, and the completion fistulogram I, the radiologist will assess if the residual stenosis is $\leq 30\%$; if this is the case then the patient will proceed to randomisation.

Randomisation will take place via a web based randomisation service, hosted at the UKCRC registered clinical trials unit at KCL. Site staff will access the service via www.ctu.co.uk using a computer in the angiography room or an office nearby. It will be performed by the radiologist performing the study procedure, or their nominee, and each randomiser will have unique user access. Access will be provided by the CTU upon the authorisation of the trial manager, once the delegation of authority form has been completed and relevant documentation regarding the individuals has been collected. Nominees must not be clinicians or nurses who may decide to refer the patient for re-intervention.

As explained in 1.1.2, patients will be randomized using minimisation; this is performed with an 80% probability of allocating to the arm which reduces the imbalance. The allocation sequence will be generated dynamically so that the next allocation will only be generated and become known upon actioning a request from the study site staff. Once randomised, the system will automatically generate an email confirmation, which will be sent to relevant study staff in a blinded or unblinded format, depending on their role in the study: an unblind email is received by the trial manager and the radiologist who is performing the randomisation; and a blind email is received by the principal investigator and research nurses.

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If it is not possible to use the randomisation system randomisation may occur using the toss of a coin in order to avoid losing the patient from the study. This should only be needed, if at all, in specific and rare situations such as the CTU server being inaccessible. This will be performed by two people with heads denoting drug-coated balloon, and tails denoting placebo. The CTU must be informed of the coin randomisation as soon as possible.

1.1.4 Duration of the treatment period

Study treatment is described in detail in the protocol section 4.5. This is a one-off treatment that is administered within one study visit. Any repeat intervention is considered an event and therefore the end of the follow up.

1.1.5 Frequency and duration of follow-up

Study assessments will take place every 3 months. Follow up will be variable but for a minimum of 1 year. These will involve a clinical assessment to take place either face-to-face or via a telephone conversation. Any face-to-face meetings will usually coincide with dialysis to avoid additional patient travel.

1.1.6 Visit windows

At the time of each 3-month study assessment, an allowance of one month will be given either side to measure follow-up. This one month visit window will be the same for recording data throughout the follow-up period.

1.1.7 Eligibility screening

Patients that may be eligible will be identified in a vascular access clinic and assessed by surgeons, specialist nurses and nephrologists. In order to confirm there is a significant stenosis prior to angiography, a duplex ultrasound is encouraged but is not mandatory. At least 24 hours after being given the patient information sheet and before entering the angiography room for the pre-procedure fistulogram, consent will be taken and eligibility criteria will be assessed.

Inclusion and exclusion criteria are described in sections 3.2 and 3.3 of the protocol.

The radiologist who will perform the pre-procedure fistulogram, high-pressure balloon fistuloplasty and completion fistulogram will be informed that the patient is potentially eligible for the study, and they will assess the remaining eligibility criteria.

1.1.8 Measures

Baseline

The following demographics will be measured at baseline:

- Age (years)
- Gender (male; female)
- Ethnicity (White; Black; Asian; Mixed; Other)

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The following clinical details will be measured at medical history screening:

- Current diabetes diagnosis (yes; no)
- Patient smoking history (current smoker; former smoker; never smoked)
- Coronary artery disease (yes; no)
- Peripheral vascular disease (yes; no)
- Time since end-stage kidney failure (months)
- Previous renal transplant(s) (number)
- Total accumulated time with a functional renal transplant (months)
- Total accumulated time patient has spent on haemodialysis (months)
- Total accumulated time patient has spent on peritoneal dialysis (months)
- Location of fistula (right arm; left arm)
- Type of native fistula (Radio-cephalic; Brachio-cephalic; Basilic vein transposition; Ulnar-cephalic)
- Time since fistula was formed (months)
- Time since fistula was first used (months)
- Current access circuit previously had a thrombosis (yes; no)
- Previous surgical interventions to the current access circuit (number)
- Previous fistuloplasties to the current access circuit (number)
- Primary indication for the index procedure (inadequate dialysis; poor fistula blood flow; prolonged bleeding; high venous pressures; low arterial pressure; difficulty needling; other evidence of fistula dysfunction)

The following clinical details will be measured at the pre-procedure fistulogram:

- Location of stenosis (juxta-anastamotic; venous segment; cephalic arch; after cephalic arch and not beyond the thoracic inlet; beyond the thoracic inlet)
- Degree of stenosis (5%)
- Length of stenosis (mm)
- Radiologist (initials)

The following clinical details will be measured at the treatment fistuloplasty:

- Index lesion vessel diameter (mm)
- Diameter of plain balloon used (mm)
- Length of plain balloon used (mm)
- Pressure to which used plain balloon was inflated (atm)
- Number of unsuccessful attempts at plain balloon fistuloplasty (0-2)
- Complications due to plain balloon fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Diameter of study treatment balloon used (mm)
- Length of study treatment balloon used (mm)
- Pressure to which study treatment balloon was inflated (atm)
- Complications of the study treatment fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Residual stenosis still 30% or less after study treatment (yes; no)

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- Further fistuloplasty performed after study treatment (yes; no)
- Type of balloon from further fistuloplasty (Dorado; other)
- Diameter of balloon from further fistuloplasty (mm)
- Length of balloon from further fistuloplasty (mm)
- Residual stenosis 30% or less after further fistuloplasty (yes; no)
- Complications due to further fistuloplasty (vessel rupture; balloon rupture; vein thrombosis; venous vasospasm; other; none)
- Radiologist (initials)

Primary outcome measures

The primary outcome measure is time to Target Lesion Primary Patency (TLPP). This will be measured in days post treatment fistuloplasty.

Secondary outcome measures

The secondary outcomes, as listed in 1.1.1, will be measured as follows:

1. Late lumen loss (mm); the difference between the diameter of the lesion at the completion fistulogram II (baseline) and at the protocol fistulogram (6 months)
2. Rate of binary angiographic re-stenosis (%); at the protocol fistulogram (6 months)
3. Time to loss of access circuit primary patency (days post treatment fistuloplasty)
4. Time to loss of access circuit cumulative patency (days post treatment fistuloplasty)
5. Procedural success (yes; no); stenosis $\leq 30\%$ at completion fistulogram II (baseline)
6. Thrombosis events (number); recorded as fistula interventions throughout the trial
7. Fistula interventions (number); recorded throughout the trial
8. Adverse events (number); recorded throughout the trial
9. Patient quality of life; EQ-5D and POS-S Renal scores

Adverse events

The following adverse event measures will be collected at 6 and 12 months post randomisation, and at withdrawal, where applicable:

- Adverse Event (Oedema of hand or arm; Pseudoaneurysm; Haematoma; Distal Ischaemia; Neurological complications; Infection localised to fistula; Central venous catheter insertions; other)
- Duration of event (days)
- Intensity (mild; moderate; severe)
- Outcome (resolved; resolved with sequelae; ongoing; death; unknown)
- Related to study intervention (definite; probable; possible; remote; none)
- Serious Adverse Event (yes; no)
- Ongoing at end of study (yes; no)

Please refer to section 2 for the schedule of assessments and measures.

1.1.9 Sample size estimation (including clinical significance)

For the definition of the survival curve in the placebo balloon group, we assumed target lesion primary patency of 61%, 42%, and 35% at 6, 12 and 24 months respectively. This was consistent with published results (Bountouris, 2014; Tessitore, 2003) and with our own audit

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data. A hazard ratio (HR) of 0.5 was chosen as the minimum clinically relevant effect size; (Katsanos, 2012) found a HR of 0.3 for Target Lesion Primary Patency at 6 months, however, the confidence interval was broad and the effect size is expected to be closer to the null when AVGs are excluded. Based on these assumptions, it is expected that the paclitaxel coated balloon group will show 78%, 65%, and 59% survival of TLPP at 6, 12 and 24 months respectively. Recruiting 211 patients, with variable follow up, a minimum follow up of 1 year, and three interim analyses, will provide 94% power to detect a statistically significant difference between the two groups in TLPP survival with 2-sided 5% type I error rate. It is expected that 108 patients will experience fistula failure during the follow up period, 66 in the control arm, and 42 in the intervention arm.

The required sample size has been estimated assuming cumulative 10% drop-out in each treatment arm by the end of the study, which would result in 6 patients in the treatment arm, and 3 in the control arm. We have planned for a recruitment rate of 2 patients per month (ppm) during the first three months, 8 ppm up to 7 months, and 12 ppm onwards. The expected accrual duration will be 22 months, and the maximum study duration (including follow-up) 34 months.

1.1.10 Brief description of proposed analyses

Analyses will be carried out by the trial statistician (ER) once the database has been locked. Data will be analysed with an intention-to-treat approach (i.e. analyse all those with data in groups as randomised irrespective of treatment received).

There will be descriptive statistics reported on the measures mentioned in 1.1.8, with an aim to comparing the treatment arms, and to review the patient demographics.

For the primary analysis, to test the superiority of the paclitaxel-coated balloon treatment group compared to placebo balloon in TLPP survival, Cox-Proportional Hazards regression will be used. This will be repeated using multivariate cox regression for the adjustment of the treatment effect size for the effect of known clinical covariates; which are listed in detail in section 1.3.2.

Effects on secondary outcomes will be analysed using the same strategy for time-to-event variables, and generalized linear models for binary and continuous outcome measures, adjusting for the effects of relevant covariates when appropriate.

Interim analysis of the primary outcome will be performed up to three times throughout the study, based on the cumulative number of failures of the treatment area.

Further details of the analyses are given later on in this document.

Data summaries and analyses will be carried out in Stata 14.0.

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1.2 Data analysis plan – Data description

1.2.1 Recruitment, eligibility and representativeness of patients

A CONSORT flow chart will be constructed – see Figure 1. The number of patients will be summarised using the following categories: total number of patients screened; eligible; consenting; and randomised.

Then by treatment arm: patients compliant and non-compliant with intervention; continuing through the trial; withdrawing; lost to follow-up; and excluded or analysed.

Compliance (adherence) is defined as receiving the following procedures: plain balloon fistuloplasty; completion fistulogram I; study treatment fistuloplasty; and completion fistulogram II.

A summary of the number of patients compliant with the study treatment will be provided and stratified by radiologist.

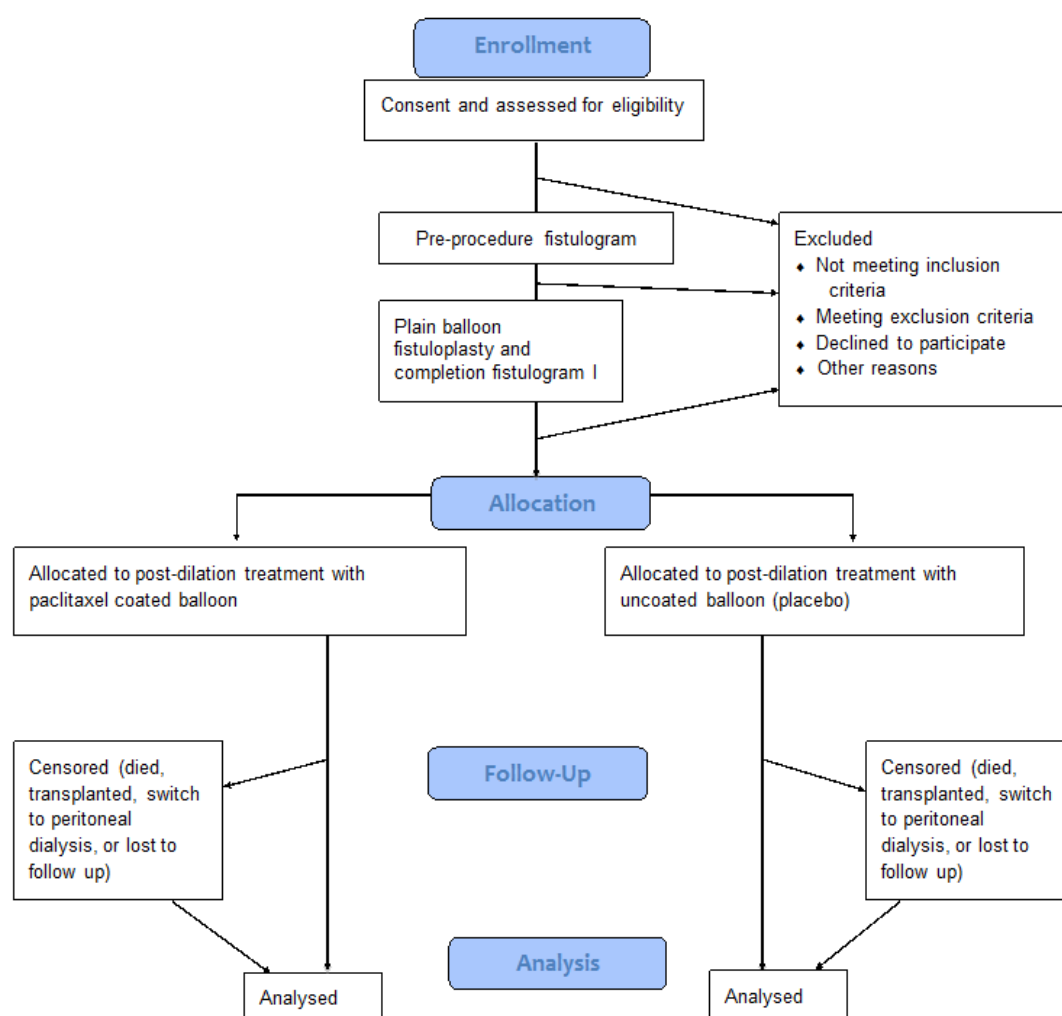


Figure 1. Template CONSORT diagram for PAVE trial

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1.2.2 Baseline comparability of randomised groups

All baseline variables listed under measures in section 1.1.8 will be reported by trial arm and overall. They will be grouped into patient demographics and patient clinical information, and reported as: minimums and maximums, means and standard deviation, medians and quartiles for continuous variables as appropriate; and frequencies and proportions for categorical variables. No significance testing will be used to test baseline differences between the trial arms.

1.2.3 Adherence to allocated treatment and treatment fidelity

Adherence to allocated treatment (compliant versus non-compliant), as described in 1.2.1, and the reasons for not completing the treatment process will be summarised using the treatment fistuloplasty form. Adherence will be compared between trial arm using baseline variables; and the reasons for withdrawal from treatment will be summarised.

1.2.4 Loss to follow-up and other missing data

Withdrawal from trial follow-up (attrition rate) will be reported by intervention group, including reasons for withdrawal. The proportions of participants missing each variable will be summarised in each arm and at each study visit.

If necessary, multiple imputation will be used for the imputation of missing values in baseline variables and secondary outcomes. Patients with TLPP at the end of follow up will be considered censored, as will those who receive a renal transplant, switch to peritoneal dialysis or are lost to follow up before the study end.

The baseline characteristics and adverse events of patients lost to follow up will be compared to those with complete follow up data. The relationship between these and missing data will be investigated graphically to see if baseline characteristics or adverse events predict missing, i.e. drop-outs are not random.

1.2.5 Adverse event reporting

Adverse events (AE), adverse reactions (AR), serious adverse events (SAE) and serious adverse reactions (SAR) will be summarised by trial arm and overall.

1.2.6 Assessment of outcome measures (unblinding)

Outcome assessors and the trial statistician are being kept blind to treatment allocation.

1.2.7 Descriptive statistics for outcome measures

The primary and secondary outcomes as listed in section 1.1.8 will be described by treatment group and time point. Means and standard deviations or medians and interquartile ranges will be used for continuous variables, where relevant; this will check whether continuous outcomes can be assumed normally distributed. Kaplan-Meier plots,

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hazard-ratio and its confidence interval will be used to describe the time to event results. Frequencies and proportions will be used to describe binary variables.

1.3 Data analysis plan – Inferential analysis

1.3.1 Aims of formal inferences

The formal statistical analyses will estimate the differences in relevant variables (time to event, quality of life) between patients randomised to the paclitaxel-coated balloon angioplasty compared to high-pressure placebo balloon angioplasty, by intention to treat.

As mentioned in section 1.2.4, for the primary outcome and other time to event variables, patients lost to follow-up will be right censored; this means they are counted as not having experienced end of target lesion primary patency, or the relevant event, for the period of time we have data on them. If dropout is related to both outcome and treatment, then dropouts may bias the results.

Group difference estimates and associated 95% confidence intervals will be reported. The trial statistician will remain blind until the main analyses have been completed. The overall significance level will be 5% (two-sided) for the primary and secondary outcomes. Significance level of final analysis of primary outcome will be determined by the alpha spending function used to plan interim analyses.

Details on the methods for handling missing data are given in sections 1.3.8.

Sensitivity analyses will be used to assess the robustness of conclusions; please refer to section 1.4 for details of the planned sensitivity and subgroup analyses.

1.3.2 Analysis of the primary outcome

The analysis population will include all patients randomised with sufficient information to carry out the analysis, i.e. complete primary outcome data and minimisation factors. The primary outcome is time to end of target lesion primary patency (TLPP); measured as days post randomisation. For the purpose of the primary outcome analysis, this will be taken as recorded by the target lesion primary patency form.

Expected time to end of TLPP will be calculated using the hazard ratio estimated by the model explained below. Survival analysis methods will be used to compare the primary outcome for the two groups as this can factor in censoring and time.

Kaplan-Meier plots will be used to graphically illustrate and compare the observed probabilities of target lesion primary patency past certain times in the trial period, taking into account censoring, for the two trial arms. This is a non-parametric estimate of the survival function over the analysis time, and will also be used to check the Cox proportionality assumption – see section 1.3.10.

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Cox-Proportional Hazards regression will be used to model the effect of predictors and covariates on the hazard rate and estimate the relative risk by trial arm. This will be compared to an initial estimate from the null model where the model will be fitted without any covariates. Model components included in the primary model will be a baseline hazard function that is unspecified but positive; previous radiological intervention in the access circuit; on haemodialysis at randomisation; trial arm; observed study time (length of time between patient entering and exiting study); and a trial arm*observed time interaction term. The interaction term allows for variable follow-up time effects.

A secondary adjusted analysis will be fit to evaluate the impact of baseline covariates on the size of the treatment effect. The covariates considered will be: baseline characteristics (ethnicity; age; diabetes diagnosis; and smoking history) and clinical variables at baseline (total time on haemodialysis; time since end stage kidney failure; type of native fistula; previous circuit intervention; and location of stenosis).

The relationship between baseline variables and missing outcome data will be assessed using logistic regression with an outcome variable that represents whether outcome data are present or missing. Should any baseline variables be predictive of missing then these will be included in the primary analysis Cox regression models as further covariates.

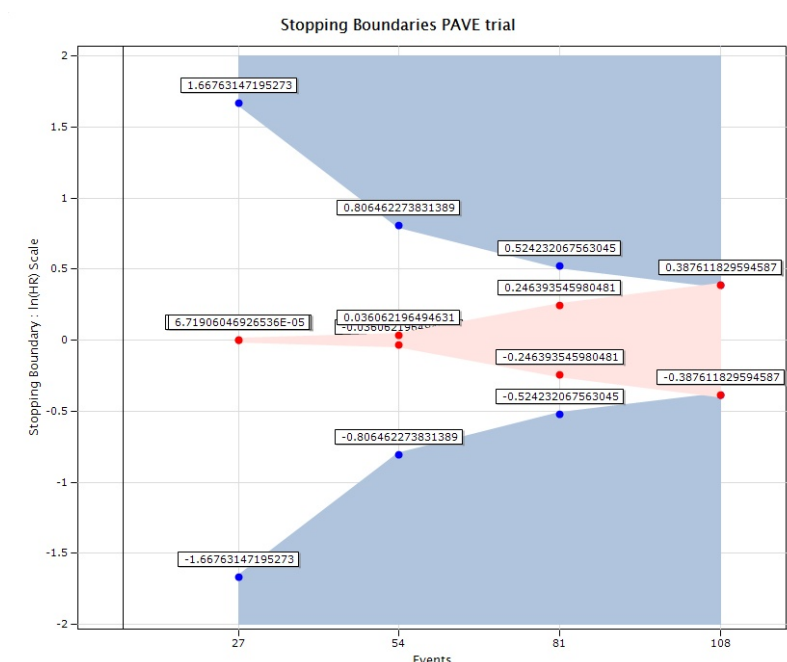
1.3.3 Interim analysis

Interim analysis of the primary outcome will be performed up to three times throughout the study, based on the cumulative number of failures in the primary outcome, i.e. after 27, 54 and 81 events, expected approximately at 9, 14 and 19 months of study under the null, and at months 11, 17, and 23 under the alternative hypothesis. Group sequential stopping boundaries have been calculated using a Lan-de-Mets spending function (with O'Brien-Fleming parameters), to allow early stopping for rejection of the null or the alternative hypotheses. Stopping in case of boundary crossing is non-binding and will be discussed with the DMEC members during a closed session that does not include any trial members who are blinded.

The Hazard Ratio used to evaluate the crossing of stopping boundaries will be calculated with a Cox-proportional hazards regression that includes presence or absence of previous interventions and currently on haemodialysis or not as covariates, as well as treatment group as independent variable of interest.

Stopping boundaries are displayed in the figure below:

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The table below shows further details of the stopping boundaries, including expected probability of crossing at each interim, and cumulative Alpha and Beta spent. Stopping boundaries in the table are expressed in the HR scale.

Look #	Info. Fraction	Events	Cum. α Spent	Cum. β Spent	Boundaries			
					Efficacy Boundary		Futility Boundary	
					Upper	Lower	Upper	Lower
1	0.25	27	0	0	5.3	0.189	1	1
2	0.5	54	0.003	0.004	2.24	0.446	1.037	0.965
3	0.75	81	0.019	0.024	1.689	0.592	1.279	0.782
4	1	108	0.05	0.059	1.473	0.679	1.473	0.679

Look #	Sample Size		Analysis Time		Incremental Boundary Crossing Probabilities					
					Under H0: $\ln(\lambda_t/\lambda_c) = 1$			Under H1: $\ln(\lambda_t/\lambda_c) = 0.49...$		
	Under H0	Under H1	Under H0	Under H1	Efficacy		Futility	Efficacy		Futility
					Upper	Lower		Upper	Lower	
1	91	106	9.483	10.968	0	0	0	0	0.006	0
2	140	163	14.522	16.985	0.002	0.002	0.105	0	0.333	0.004
3	185	211	19.213	22.651	0.008	0.008	0.633	0	0.44	0.02
4	211	211	23.95	33.792	0.014	0.014	0.214	0	0.162	0.035

Test statistics for interim analysis will be calculated with standard statistics software packages (R or Stata).

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Interim analyses will be programmed by the trial statistician, and run and using the partially blinded randomisation sequence (trial arm numbers 1 or 2). The results will be presented to the DMEC in a partially blind report, and full unblinding of the code will only be provided to the members if they request it.

1.3.4 Analysis of secondary outcomes

Secondary patient outcomes relating to time-to-event variables, for example, time to end of access circuit primary patency, will be analysed using Cox regression models in a similar method to above.

Continuous variables such as POS-S Renal score for quality of life, will be checked for normality, transformed if necessary and analysed using linear regression models. Otherwise, they will be analysed using a Wilcoxon-signed-rank test for independent samples. Logistic regression models will be used for binary secondary outcomes, for example, procedural success (rate of binary angiographic re-stenosis $\geq 50\%$) at the six month protocol fistulogram.

Similarly to the primary outcome analysis, covariates considered in the models will include: baseline measure of outcome variable, where applicable; minimisation factors; trial arm; and time in study. An interaction term will also be included between observed study time and study treatment, as above.

1.3.5 Stratification and clustering

Randomisation is on the patient level, minimising on radiologist performing the study treatment and previous radiological intervention to treatment area or not; therefore these variables will be included as covariates in the modelling process, as mentioned in section 1.3.2. However, the data should not have a clustered structure so this does not need to be accounted for.

1.3.6 Missing items in scales and subscales

The number (%) with complete data will be reported. The ideal approach would be to use missing value guidance provided for scales.

1.3.7 Missing baseline data

We do not anticipate missing values in pre-randomisation variables. However, if we encounter missing baseline values then these can be singly imputed without incurring bias of the treatment effect estimate (White & Thompson, 2005).

1.3.8 Censoring and missing outcome data

For time to event outcomes, patient data is considered censored when the patient is withdrawn from follow-up, i.e. it is only known that the amount of time to event for that patient is greater than some value. Censoring will also happen at the end of the study, if the patient does not experience the primary endpoint before end of follow-up. In the analysis,

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the censored observations will be included in the number of patients at risk in respect to their observed study time (survival time).

For non-time to event outcomes, missing post-randomisation assessments will be dealt with by fitting generalised linear models to all the available data using maximum likelihood methods. Such an approach provides valid inferences under the assumption that the missing data mechanism is ignorable (or MAR). This allows for missingness at later times to be predicted by outcome values at earlier times. However, if post treatment variables such as compliance with study procedures are found to be predictive of drop out, multiple imputation will be considered.

1.3.9 Method for handling multiple comparisons

Analysis of secondary outcomes is considered exploratory, and therefore there will be no correction for multiple testing. However, care should be given to the interpretation of inference for the numerous secondary outcomes and it may be necessary to assess the agreement between similar outcome measures. Cohen's Kappa statistic and/or Spearman's rank correlation coefficients may be used to test for inter-participant reliability and to measure the degree of linear association between two outcomes. For example, angiographically determined late lumen loss and the rate of binary angiographic re-stenosis would be expected to be highly predictive of one another.

1.3.10 Method for handling non-compliance

In addition to the primary intention-to-treat analysis the effect of actually receiving treatment as defined in the protocol will also be estimated.

There is not expected to be a problem with non-compliance due to the design of the trial.

1.3.11 Model assumption checks

In order to assess the adequacy of the Cox regression models for the primary outcome and time-to-event secondary outcomes, the main assumption to test for is proportionality; the Kaplan-Meier plots will be used to check if the curves for the two trial arms are the same shape, and if the separation of the curves remains proportionate throughout the analysis period.

In addition, time-dependent covariates will be generated by creating interactions of the predictors and function of survival time; if these are significant then the predictors are not proportional.

If the assumption for proportionality is violated then the consequence this has on the results can be checked. The Cox model can be stratified according to the variables with non-proportional hazards to see whether that changes the hazard ratios for the variables of interest; if it still does, then it may be necessary to use an alternative model. One parametric alternative is the Royston-Parmar model, which is more flexible and can fit a non-proportional hazards model.

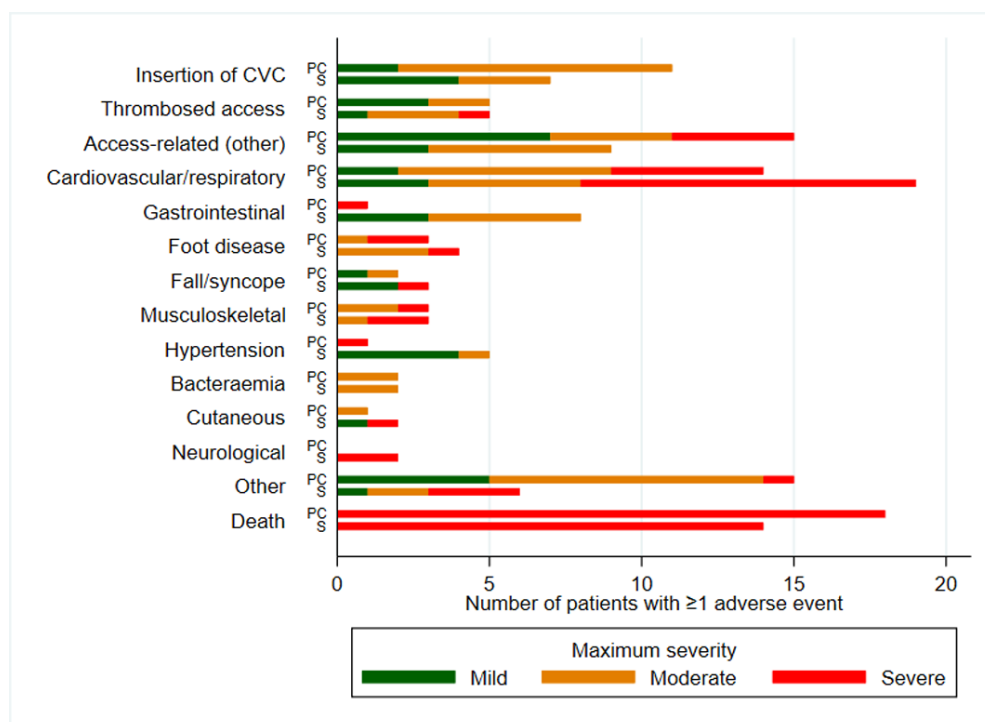


Figure 3.

Severity and type of adverse event by treatment group. PC: paclitaxel-coated balloon group; S: standard balloon group. This bar chart illustrates the main types of adverse events that were reported by patients during follow-up, by treatment group and maximum severity. Patients can be included in more than one type of event, but if they experienced a certain event type more than once, then they have only been counted once for that event, and the maximum severity that they reported for that type of event has been used. Please note: this graph does not include deaths that occurred after patients formally withdrew from the trial; CVC: central venous catheter.

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For the other secondary outcomes regression residuals will be plotted to check for normality and outliers, where applicable.

1.4 Sensitivity analyses

1.4.1 Planned sensitivity analyses

A sensitivity analysis will be performed using adjudicated data from the core lab readings, in comparison to the primary analysis where the events reported in the trial will be used. This will assess the robustness of the trial findings by clarifying whether the primary analysis conclusions are impacted by any methodological issues, such as outcome definitions.

1.4.2 Planned subgroup analyses

Subgroup analyses will be carried out to assess whether the observed effect is consistent across patient categories; to do this, an interaction term will be included in the Cox proportional hazards model between the exposure (study treatment group) and the subgroup variable.

The planned subgroups will be: second minimisation factor (previous radiological intervention to the treatment area or not); smoking history (current smoker, former smoker, never smoked); baseline diabetes diagnosis (yes, no); current total time on haemodialysis (quartiles); total time since end stage kidney failure (quartiles); type of native fistula (Radio-cephalic, Brachio-cephalic, Basilic vein transposition, Ulnar-cephalic); and location of stenosis (juxta-anastomotic, venous segment, cephalic arch, between cephalic arch and thoracic inlet).

1.4.3 Competing risks analyses

To assess the influence of events that may prevent other events from being observed, competing risks analyses will be planned to adjust for these. Specifically, 'irrelevant' deaths and re-transplantations will be defined as competing risks rather than censored events. The cause of death will be checked from hospital notes and/or death certificates.

1.4.4 Exploratory analyses

This analysis plan does not cover secondary exploratory analysis. Exploratory mediator and moderator analyses may be performed after the primary trial data analysis.

1.5 Software

Data management: An online data collection system for clinical trials (MACRO; InferMed Ltd) will be used. This is hosted on a dedicated server at KCL and managed by the KCTU. The KCTU Data Manager will extract data periodically as needed and requests will usually be made by the trial statistician. There will be several database extracts throughout the trial for each DMEC Report, and a final extract after data lock. Data will be provided in comma separated (.csv) format.

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Statistical analysis: Stata and or R will be used for data description and inferential analysis.

1.6 Changes to version

- 1 Since Version 1.0 the Trial Manager(s) have changed, and this has been updated
- 2 Due to the recruitment period taking longer than planned, and including more hospital sites than originally expected, clarification has been made to the following sections in relation to minimisation factors, duration of trial follow-up, and frequency of interim analysis:
 - 1.1.2
 - 1.1.5
 - 1.1.6
 - 1.1.10
 - 1.2.1
 - 1.3.2
 - 1.3.3
 - 1.3.8

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2 SCHEDULE OF ASSESSMENTS AND MEASURES

	Variable count	Enrolment	Treatment day (Day 0)	Day 1-3	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	Month 27	Month 30	Month 33	Month 36	Ongoing
01. Registration form	5	X															
02. Eligibility form	14	X															
03. Medical History form	19	X															
04. Haematology and Biochemistry form	11	X		X	X	X											
05. Pre-procedure Fistulogram form	8		X														
06. Randomisation form	4		X														
07. Treatment Fistuloplasty form	46		X														
08. Fistula Intervention form (repeating)	32																X
09. Month 6 Fistula Function form	9					X											
10. Protocol Fistulogram form	11					X											
11. POS-S Renal questionnaire	25	X				X		X									
12. EQ-5D questionnaire	6	X				X		X									
13. Medications form	17	X			X	X	X	X	X	X	X	X	X	X	X	X	
14. Adverse Events form	9																X
15. Withdrawal form	5																X
16. Status form	5				X	X	X	X	X	X	X	X	X	X	X	X	
17. Loss of Patency form (repeating)	9																X

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3 References

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